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(57) Abstract

2-Thioindoles (2-selenoindoles) and analogous 2-indolinethione (2-indolineselenone) and polysulfide (selenide) compounds, salts thereof, methods of production, intermediates in their production, pharmaceutical compositions containing said compounds, and methods for inhibiting protein kinase dependent disease in a mammal or treating aberrant cell growth in a mammal, using said compositions, are disclosed.

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2-THIOINDOLES (SELENOINDOLES) AND RELATED DISULFIDES (SELENIDES) WHICH INHIBIT PROTEIN TYROSINE KINASES AND WHICH HAVE ANTITUMOR PROPERTIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of co-pending application U.S. Serial Number 926,015, filed August 6, 1992.

FIELD OF INVENTION

The present invention relates to substituted 2-thioindoles (selenoindoles) and other related compounds, which we have unexpectedly found to be potent inhibitors of the epidermal growth factor receptor tyrosine kinase (EGF-TK) and other protein tyrosine kinases, and which show antitumor activity. The invention also relates to use of the compounds as inhibitors of protein tyrosine kinases and as antitumor agents.

BACKGROUND OF THE INVENTION

Protein phosphorylation is a critical mechanism for regulating protein function in the signal transduction pathway in normal and transformed cells. Protein tyrosine kinases (PTK) are an important class of phosphorylating enzymes which mediate this signalling and thereby regulate cell growth and proliferation. PTKs catalyze the transfer of the terminal phosphate from ATP to the phenol of tyrosine in substrate proteins. Some growth factor receptors,

protooncogenes and oncogene products possess PTK activity. The overexpression or inappropriate expression of normal or mutant kinases can result in the loss of growth control and the unregulated cell proliferation associated with malignancy. Small molecules which selectively inhibit these enzymes are, therefore, of therapeutic interest as mediators of cell growth and as antitumor agents.

In some growth factor dependent tumors, the growth factor signal transduction pathway employs the intrinsic tyrosine kinase activity of the growth factor receptor for autophosphorylation and the phosphorylation of specific cellular proteins involved in mitogenesis and cell proliferation. Specific inhibitors of PTKs have been identified previously. It has been previously demonstrated that by uncoupling the PTK from the signal transduction pathway, inhibitors of the growth factor receptor tyrosine kinases result therapeutically in antitumor activity. This antitumor activity has been demonstrated both in vitro and in vivo. Most known tyrosine kinase inhibitors are styrene-like small molecules in which the aromatic ring is hydroxylated, resembling tyrosine itself.

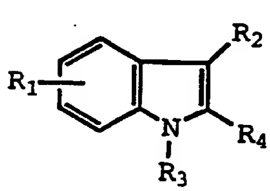
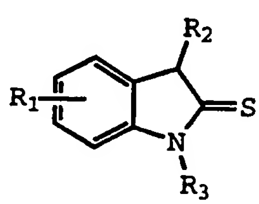
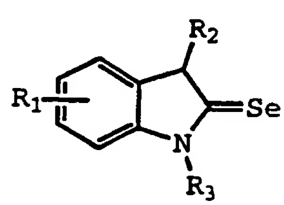
For example, the EGF-TK inhibitor erbstatin is reported to inhibit the growth of human epidermoid carcinoma A431 cells with an IC_{50} = 3.6 μg/mL (J. Antibiot. 1986;39:170). Erbstatin also inhibits the growth of the human mammary carcinoma MCF-7 and some esophageal tumors in nude mice in a dose-dependent manner (Eur. J. Cancer 1990;26(6):722 and Japanese Patent 03,109,323). Another class of PTK inhibitor called the tyrphostins also potently inhibited the EGF-dependent growth of A431 cells in vitro (J. Med. Chem. 1989;32:2344; J. Med. Chem. 1991;34:1896). The antitumor activity of two tyrphostins has been verified in vivo in nude mice bearing human squamous cell

carcinoma MH-85 (Cancer Res. 1991;51:4430). In vitro and in vivo antitumor activity against A431 tumors has also been reported for a series of sulfonylbenzoyl nitrostyrenes (J. Med. Chem. 1991;34:2328) as TK inhibitors (J. Med. Chem. 1991;34:2328 and Helv. Chim. Acta 1992;75:696).

SUMMARY AND DETAILED DESCRIPTION

In one aspect, the invention relates to 2-thioindole (selenoindoles) and other related compounds that are potent inhibitors of epidermal growth factor receptor tyrosine kinase and other protein tyrosine kinases, and which have antitumor activity. Thus, the compounds are useful in dosage form as inhibitors of protein tyrosine kinases and as antitumor agents.

More particularly, the invention comprises 2-thioindole, 2-indolinethione, polysulfide, 2-selenoindole, 2-indolineselenone, and selenide compounds represented by the general Formulas I, IV, and XXXII

 I  IV  XXXII

and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OCOR, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

C_{2-4} alkyl,
$(CH_2)_nCOOH$,
$(CH_2)_nCOOR$,
$(CH_2)_nCOR$,
$(CH_2)_nSO_2R$,
$(CH_2)_nSO_2NRR$,
$(CH_2)_nSO_2NHR$,
CH=CHCOOH,
$(CH_2)_nCH(OH)\text{-}COOH$,
$(CH_2)_nCH(NH_2)\text{-}COOH$,
$(CH_2)_nCONH_2$,
$(CH_2)_nCONHR$,
$(CH_2)_nCONRR$,
$(CH_2)_nCONHCH_2Ph$,
CONHR,
CONRR,
CONHPh,
COY,
COPhCOOH,
COPhCOOR,
$(CH_2)_nCONHPh$,
$(CH_2)_nCONHPhR$,
SO_2Y;

n is an integer from 1 to 4;

R is lower alkyl, preferably C_{1-4} alkyl;

R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SH, S_oX, S_oQ, SeH, Se_oX, and Se_oQ, where o is 1, 2, or 3, X is a member selected from H,

lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl or 2-selenoindolyl moiety of Formula I provided that the group does not comprise compounds having the names

2-(2-thioxo-3-indolinyl)acetic acid,
2-(1-methyl-2-thioxo-3-indolinyl)acetic acid,
methyl 2-(2-thioxo-3-indolinyl)acetate,
ethyl 2-(1-methyl-2-thioxo-3-indolinyl)acetate,
bis[methylindolinyl-3-acetate-(2)]disulfide,
bis[indolyl-3-acetic acid-(2)]disulfide,
bis[methylindolyl-3-acetate-(2)]trisulfide, and
bis[1-methylindolyl-3-acetic acid-(2)]disulfide.

In another aspect, the invention relates to indolinethione compounds of the above Formula IV which exist as tautomers of compounds of Formula I wherein R_4 represents SH or indolineselenone compounds of the above Formula XXXII which exist as tautomers of compounds of Formula I wherein R_4 represents SeH. The invention comprises the thione or selenone compounds in their racemic and optical isomer forms. The thione or selenone compounds produced in the (±) form can be resolved as their (+) and (-) enantiomorphic optical isomers by per se art-recognized conventional means such as fractional crystallization of salts formed from optically active acids, separation of the isomers by chiral chromatography, or the chiral catalytic reduction of precursors.

In another aspect, the invention relates to pharmaceutical compositions useful for inhibition of protein tyrosine kinases and for antitumor activity containing as an active agent in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound selected from 2-thioindole, 2-indolinethione, polysulfide, 2-selenoindole,

2-indolineselenone or selenide compounds represented by the above Formulas I, IV, and XXXII and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OCOR, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

lower alkyl, preferably C_{1-4} alkyl,
$(CH_2)_nCOOH$,
$(CH_2)_nCOOR$,
$(CH_2)_nCOR$,
$(CH_2)_nSO_2R$,
$(CH_2)_nSO_2NRR$,
$(CH_2)_nSO_2NHR$,
CH=CHCOOH,
$(CH_2)_nCH(OH)\text{-}COOH$,
$(CH_2)_nCH(NH_2)\text{-}COOH$,
$(CH_2)_nCONH_2$,
$(CH_2)_nCONHR$,
$(CH_2)_nCONRR$,
$(CH_2)_nCONHCH_2Ph$,
CONHR,
CONRR,
CONHPh,
COY,
COPhCOOH,
COPhCOOR,
$(CH_2)_nCONHPh$,
$(CH_2)_nCONHPhR$,
SO_2Y;

n is an integer from 1 to 4;

R is lower alkyl, preferably C_{1-4} alkyl;

R_3 is a member selected from H, lower alkyl and benzyl;

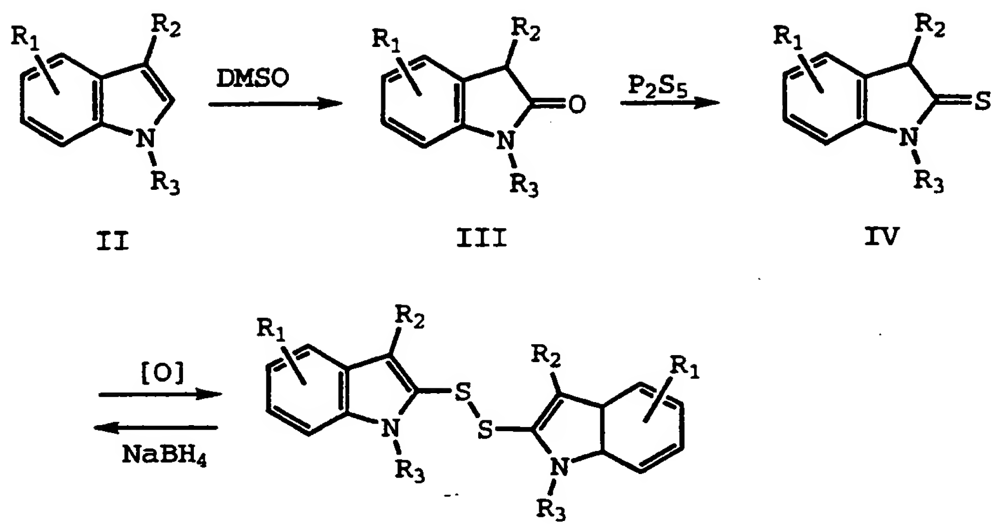
Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SH, S_oX, S_oQ, SeH, Se_oX, and Se_oQ, where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl or 2-selenoindolyl moiety of Formula I.

The invention comprises salt compounds formed by the basic or acidic thioindole compounds of the invention which form pharmaceutically acceptable salts with both organic and inorganic acids and/or organic and inorganic bases. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, isethionic, and the like. Examples of suitable bases for salt formation are sodium and potassium carbonate, sodium and potassium hydroxide, ammonia, triethylamine, triethanolamine, and the like.

The compounds of Formulas I, IV, and XXXII can be prepared by the processes described in the following Reaction Schemes 1-11.

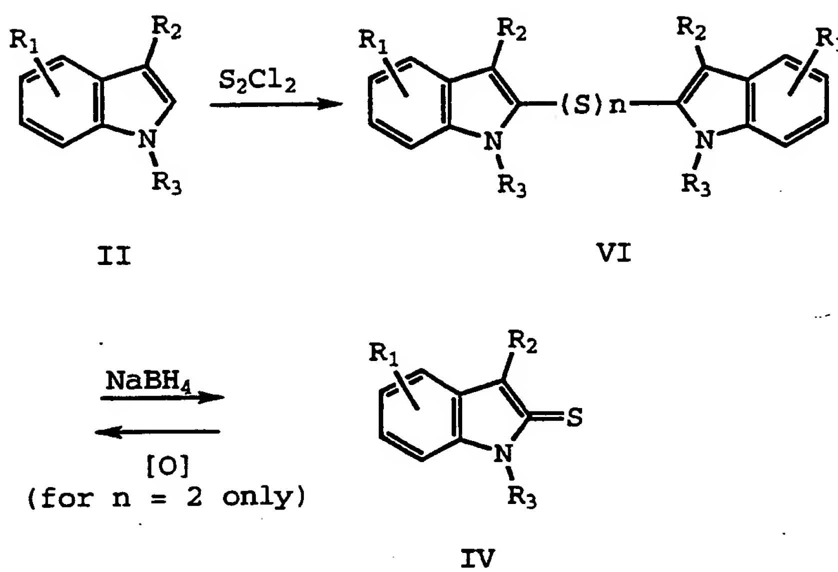
SCHEME 1



V

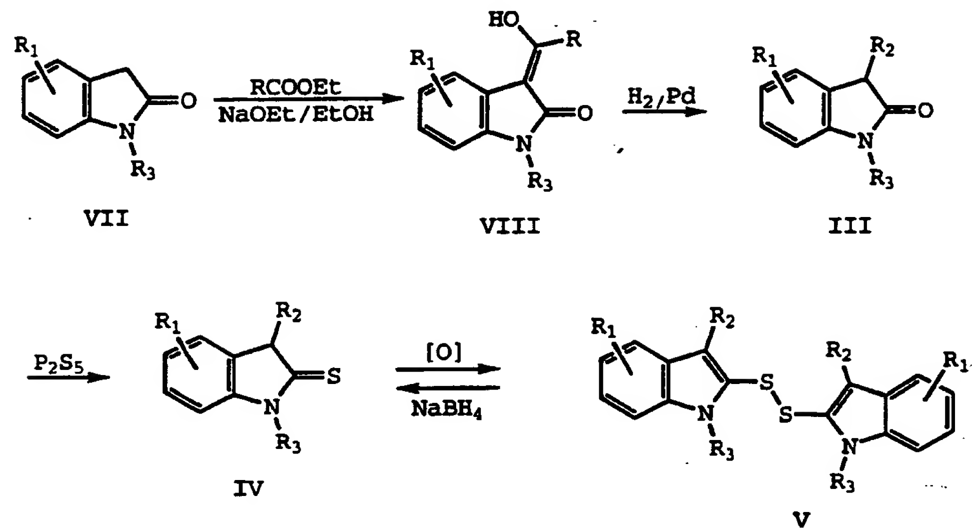
In Scheme 1, R_1-R_3 are as designated for Formula I. Oxidation of 3-substituted indoles **II** in DMSO/HCl gives good yields of 3-substituted indolin-2-ones **III** which are thiated (preferably with P_2S_5 and $NaHCO_3$ or Na_2CO_3) to yield 3-substituted 2-indolinethiones **IV**. These compounds can be converted to the corresponding disulfides V by treatment with mild oxidizing agents (e.g., $FeCl_3$), and also undergo spontaneous oxidation to **V** in solution in air.

SCHEME 2



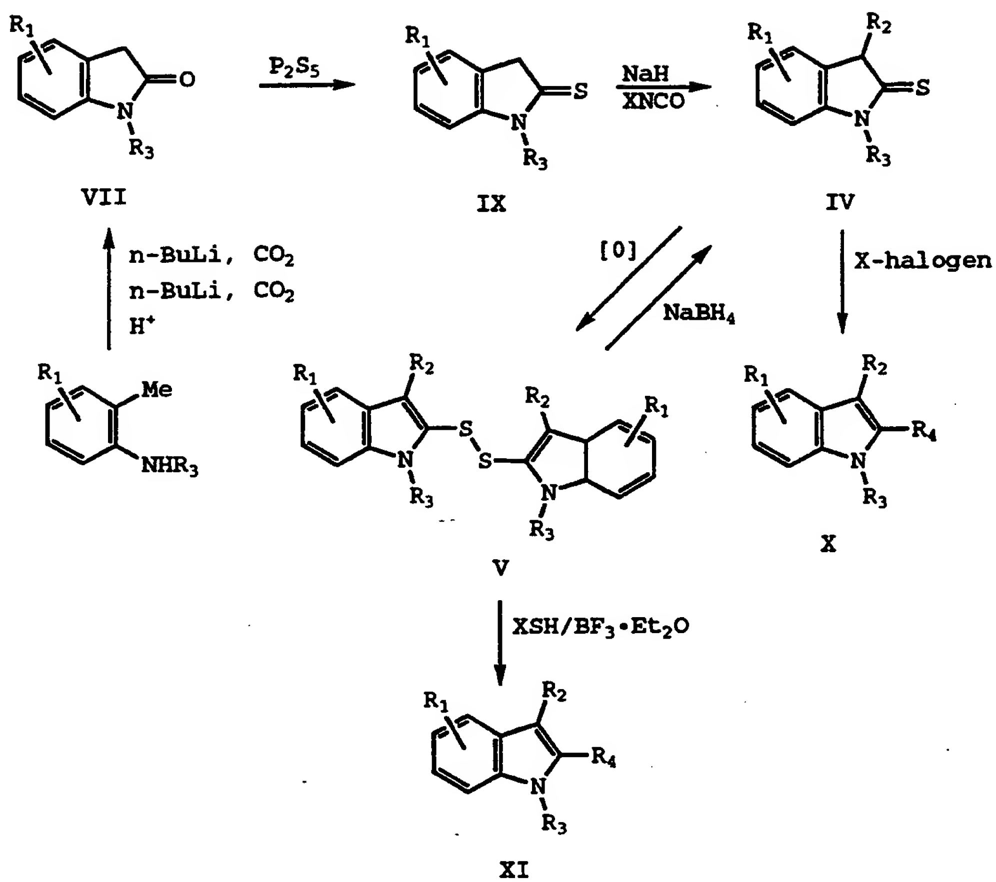
In Scheme 2, R_1-R_3 are as designated for Formula I. Treatment of 3-substituted indoles **II** with S_2Cl_2 gives mixtures of dimeric sulfides **VI**, where n = 1-3. These can be separated by chromatography, or more conveniently reduced to 2-indolinethiones **IV** with a mild reducing agent (preferably $NaBH_4$).

SCHEME 3



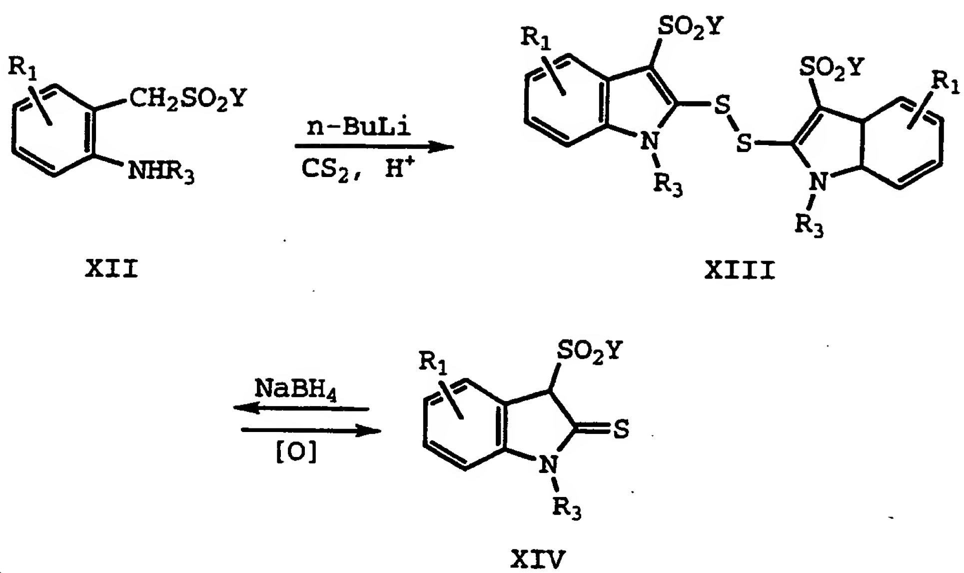
In Scheme 3, R_1-R_3 are as designated for Formula I, and R represents $(CH_2)_nCOOH$, $(CH_2)_nCOOX$, $(CH_2)_nCONHX$, $(CH_2)_nSO_2X$, or $(CH_2)_nSO_2NX$, where n is from 0 to 4, and X is as designated for Formula I. Treatment of 2-indolinones **VII** with diesters gives moderate yields of the isatylidene compounds **VIII**, which can be hydrogenated under acidic conditions to the 3-substituted indolin-2-ones **III**. Treatment of these as in Scheme 1 gives the desired compounds.

SCHEME 4


VII
IX
IV
P2S5
NaH
XNCO
n-BuLi, CO2
n-BuLi, CO2
H+
[O]
NaBH4
X-halogen
V
X
XSH/BF3•Et2O
XI

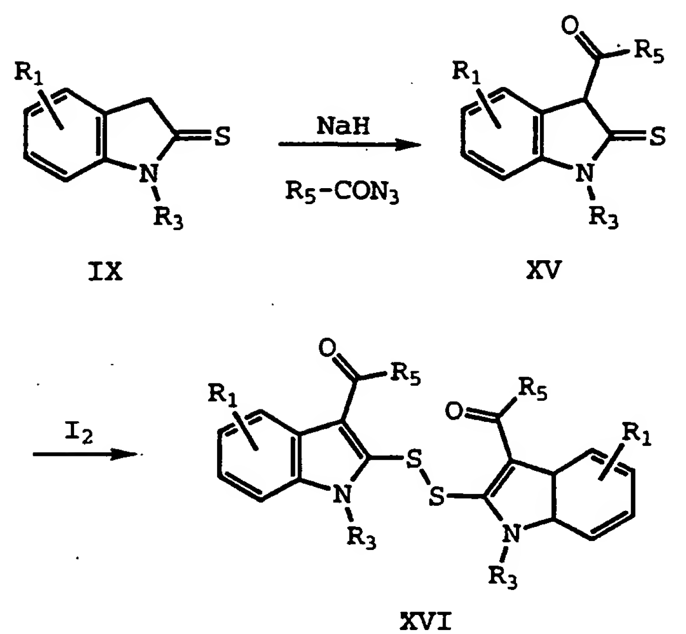
In Scheme 4, R_1-R_4, R and X are as designated for Formula I (except that X is not H). The ring-substituted oxindoles can be prepared by lithiation of the appropriately substituted ortho-toluidine derivatives, using CO_2 as both the N-protecting group and electrophile (Katritzky, Fan, Akutagawa, Wang, Heterocycles 1990;30:407). 2-Indolinones **VII** are thiated (preferably with P_2S_5 and $NaHCO_3$ or Na_2CO_3) to yield 2-indolinethiones **IX**. These compounds are deprotonated (typically with NaH in THF), and treated with an isocyanate to give 3-substituted 2-indolinethiones **IV** (where R_2 = CONHX). These compounds can be converted to the corresponding disulfides **V** as described in Scheme 1. The 3-substituted 2-indolinethiones **IV** can also react with alkylating agents (typically alkyl halides R-halogen) to give (**X**: where R_4 = X). Reaction of **V** with XSH gives mixed disulfides (**XI**: where R_4 = SSX).

SCHEME 5



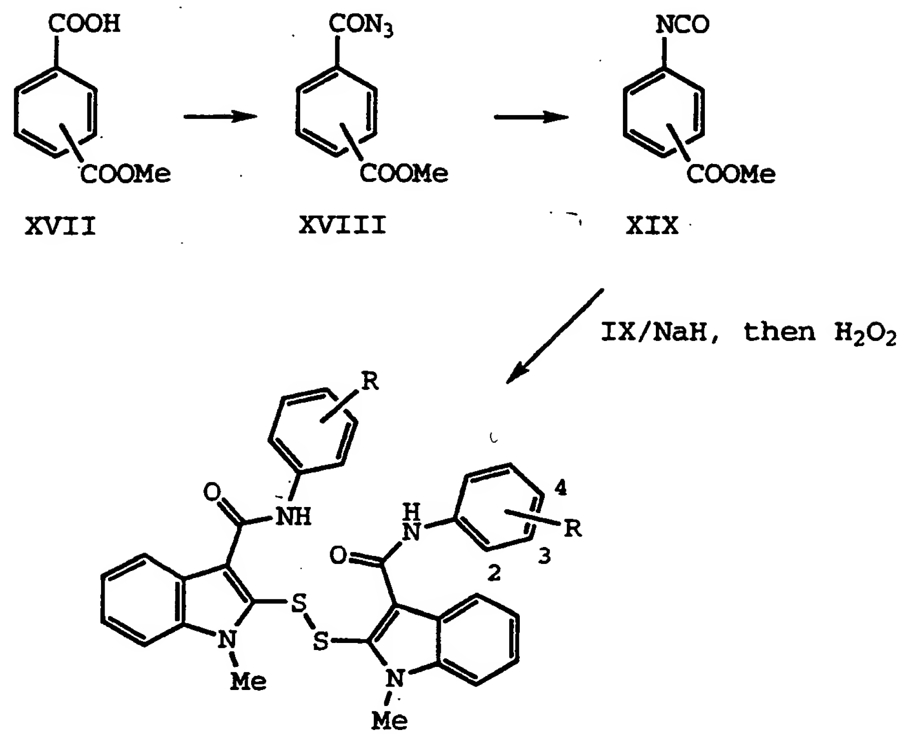
In Scheme 5, R_1 and R_3 are as designated for Formula I and Y represents lower alkyl or a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring, optionally substituted with a lower alkyl, COOH, OH, NH_2, CONHR, OR, O, or NHR group. 2-Sulfonylmethyl anilines **XII** are treated sequentially with n-butyllithium and CS_2, to give the disulfides **XIII**, which can be reduced to 2-indolinethiones **XIV** with a mild reducing agent (preferably $NaBH_4$).

SCHEME 6



In Scheme 6, R_1 and R_3 are as designated for Formula I. Deprotonation of substituted 2-indolinethiones **IX** (typically with NaH in THF), followed by treatment with an acyl azide, gives 3-acyl-substituted 2-indolinethiones **XV**, where R_5 represents H, lower alkyl, benzyl, or a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a COOH, OH, NH_2, CONHR, OR, NHR, or NRR group. Compounds **XV** can be converted into the disulfides **XVI** on mild oxidation (typically by treatment with I_2 or H_2O_2).

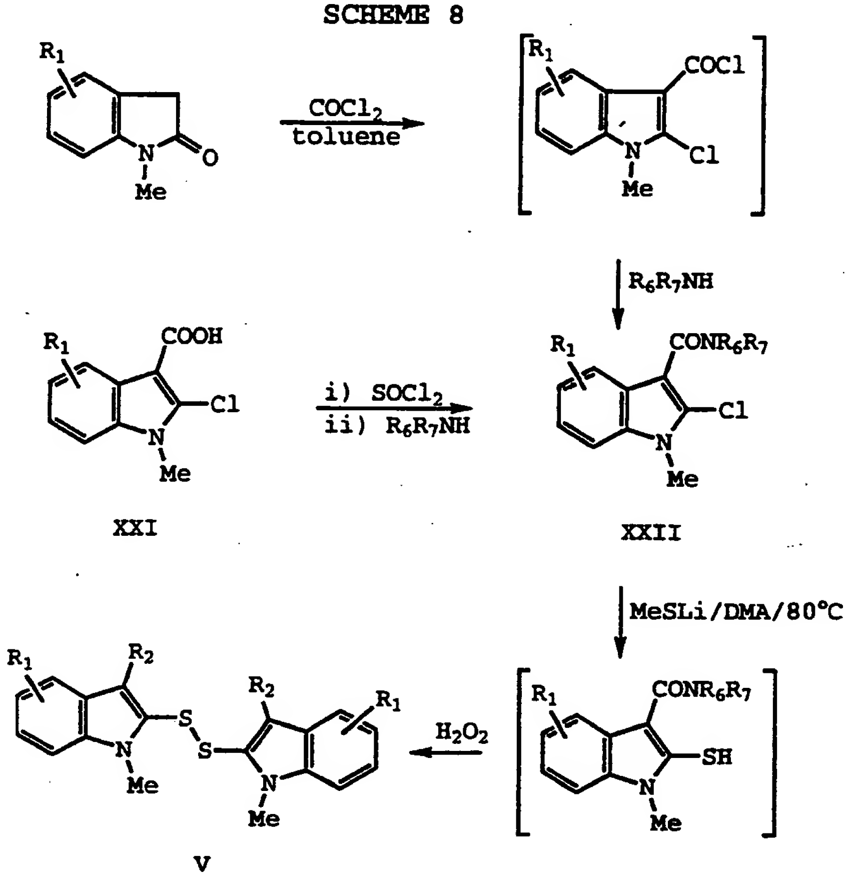
SCHEME 7



XX

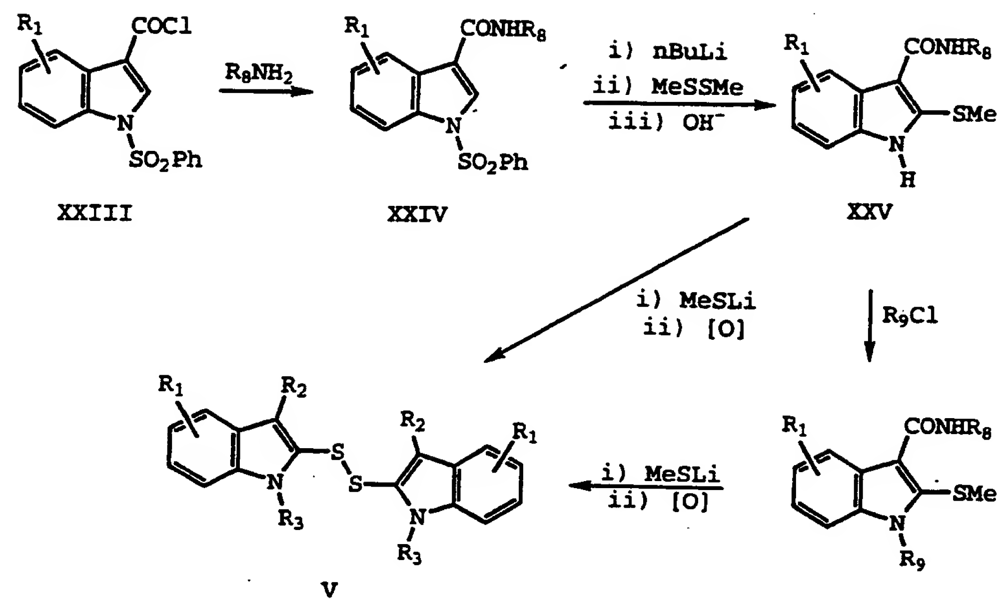
In Scheme 7, R is as designated for Formula I. Substituted aromatic and heteroaromatic acids (e.g., XVII) are converted to the corresponding acid chlorides (preferably with $SOCl_2$), and then to the corresponding acyl azides (e.g., XVIII) with NaN_3. Rearrangement to give the isocyanates (e.g., XIX) is carried out in an inert solvent (preferably toluene or xylene). These isocyanates (e.g., XIX) are converted to the disulfides (XX) by reaction with the sodium salt of 1-methyl-2-indolinethiones as outlined in Scheme 4. In suitable cases, hydrolysis of esters (XX; R = COOMe) with a mild base (preferably K_2CO_3) gives the corresponding acids (XX; R = COOH).

SCHEME 8



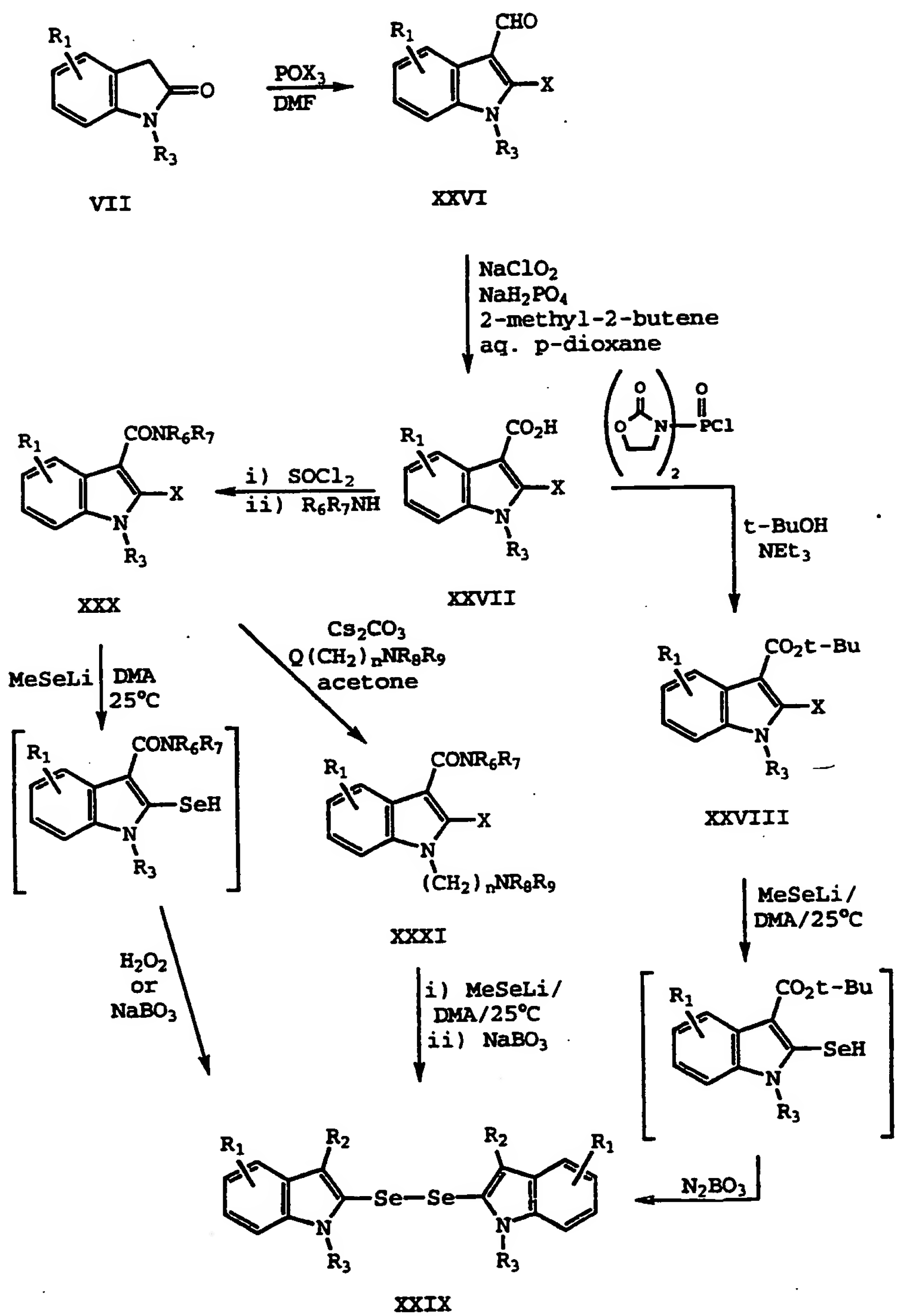
In Scheme 8, R_1 and R_2 are as designated for Formula I, and R_6 and R_7 are individually H, lower alkyl, benzyl, or a benzene ring optionally substituted with up to two of the groups COOH, OH, NH_2, CONHR, OR, NHR, or NRR. 2-Chloro-1-methylindole-3-carbonyl chloride, prepared either from indolin-2-one and $COCl_2$ or from 2-chloro-1-methylindole-3-carboxylic acid (XXI) and $SOCl_2$, is reacted with amines HNR_6R_7 or their salts, in an inert solvent (preferably 1,2-dichloroethane or CH_2Cl_2) and a base, if necessary, to give the amides (XXII). These compounds are heated with MeSLi in polar aprotic solvents (preferably dimethylacetamide) in an inert atmosphere to give intermediate thiol carboxamides, which are oxidized, (preferably with H_2O_2) to give the desired disulfides (V).

SCHEME 9



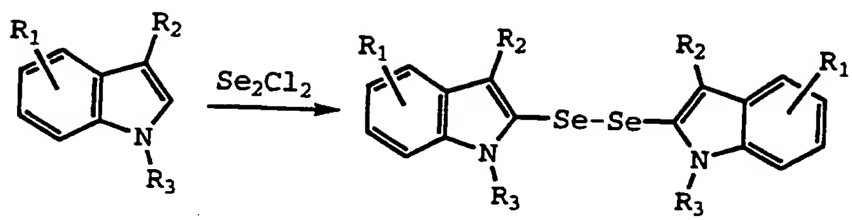
In Scheme 9, R_1, R_2, R_3, and R are as designated for Formula I. Reaction of acid chloride (XXIII) with amines gives amides (XXIV), where R_8 represents H, lower alkyl, benzyl, or a benzene ring optionally substituted with up to two of the groups COOH, OH, NH_2, CONHR, OR, NHR, or NRR. Compounds (XXIV) can be converted to 2-thioindoles (XXV) by lithiation and quenching with methyl sulfide, followed by base hydrolysis (preferably with K_2CO_3). The 2-thioindoles (XXV) can be converted to the desired disulfides (V) by dealkylation (preferably with lithium thiomethoxide) and mild oxidation (preferably with I_2 or H_2O_2). Compounds (XXV) can also be alkylated with an alkyl halide (e.g., R_9Cl), where R_9 represents lower alkyl, benzyl, or benzyl optionally substituted with up to two of the groups COOH, OH, NH_2, CONHR, OR, NHR, or NRR, and a base (preferably K_2CO_3).

SCHEME 10


R1
O
N
R3
POX3
DMF
VII
CHO
X
XXVI
NaClO2
NaH2PO4
2-methyl-2-butene
aq. p-dioxane
CO2H
XXVII
PCl
t-BuOH
NEt3
CONR6R7
i) SOCl2
ii) R6R7NH
XXX
Cs2CO3
Q(CH2)nNR8R9
acetone
CO2t-Bu
XXVIII
MeSeLi
DMA
25°C
SeH
(CH2)nNR8R9
XXXI
MeSeLi/
DMA/25°C
H2O2
or
NaBO3
i) MeSeLi/
DMA/25°C
ii) NaBO3
R2
Se
N2BO3
XXIX

In Scheme 10, R_1 is as designated for Formula I and R_6 and R_7 are individually H_1 lower alkyl, benzyl, or a benzene ring optionally substituted with up to two of the groups COOH, OH, NH_2, CONHR, OR, NHR, or NRR. R_3 is H or lower alkyl, and X = any halogen, preferably bromine or chlorine. Substituted 2-halo-3-indole carboxylic acids XXVII, prepared by oxidation of corresponding substituted 3-carboxaldehydes, are reacted with amines HNR_6R_7 or their salts in an inert solvent (preferably 1,2-dichloroethane or CH_2Cl_2) and a base, if necessary, to give the amides XXX. These compounds are reacted with MeSeLi in polar aprotic solvents (preferably dimethylacetamide) to give intermediate selenol carboxamides, which are oxidized with H_2O_2 or $NaBO_4$ to give the desired diselenides XXIX. Alternatively, intermediate XXX, where R_3 = H, can be reacted with a haloalkyl amine, or its salt, where Q = Cl, Br, I (preferably Cl) and R_8, R_9 are as defined in Formula I, but preferably R_8 and R_9 are H, alkyl, cycloalkyl, and n = 1-4 in a polar solvent (preferably acetone) and anhydrous metal carbonate (preferably cesium carbonate) to give intermediate XXXI which is converted to diselenide XXIX as described above for intermediate XXX. Additionally, intermediate acid XXVII can be converted to the substituted 2-halo-3-indole carboxylic acid tertiary butyl ester XXVIII, which can be further reacted with MeSeLi as described above for intermediate XXX to give the target substituted diselenide XXIX where R_2 = COO-tertiarybutyl.

SCHEME 11



II

XXIX

In Scheme 11, R_1-R_3 are as designated for Formula I. Treatment of 3-substituted indoles II with Se_2Cl_2 gives the diselenide XXIX.

As indicated, the compounds of this invention that are basic can form acidic salts and those that are acidic can form basic salts. All such salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply be contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, nonaqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation followed by filtration, by evaporation of the solvent, or in the case of aqueous solutions, by lyophilization, as appropriate.

The compounds of this invention are readily adapted to therapeutic use for the control of tyrosine kinase dependent diseases in mammals. Tyrosine kinase dependent diseases comprise hyperproliferative disorders which are initiated and/or maintained by aberrant tyrosine kinase enzyme activity. Tyrosine kinase inhibitors can therefore have beneficial therapeutic effects against aberrant cell growth disorders such as various cancers, atherosclerosis, angiogenesis (tumor growth/metastasis, diabetic retinopathy, for example), viral diseases (HIV infections, for example), and the like.

Tyrosine kinase dependent diseases further comprise cardiovascular diseases which are related to aberrant tyrosine kinase enzyme activity. Tyrosine kinase inhibitors can therefore have beneficial therapeutic effects against such cardiovascular diseases as restenosis. It should be understood that restenosis is an example of a cardiovascular disease which is dependent upon tyrosine kinase; one skilled in the art, however, will be aware of other examples of cardiovascular diseases which are dependent upon tyrosine kinase.

The compounds are administered either orally or parenterally, or topically as eye drops, in dosages ranging from about 0.1 to 10 mg/kg of body weight per day in single or divided doses. Of course, in particular situations, at the discretion of the attending physician, doses outside of this range will be used.

The compounds of this invention can be administered in a side variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, elixirs, syrups, injectable or eye drop solution, and the like. Such carriers include solid diluents or fillers, sterile aqueous media, and various nontoxic organic solvents.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate, and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid, and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin, and acacia. Additionally, lubrication agents such as magnesium stearate, sodium lauryl sulfate, and talc are often very useful for tableting purposes. Solid compositions of similar type are also employed as fillers in soft- and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents, and/or suspending agents as well as such diluents as water, ethanol,

propylene glycol, glycerin, and various like combinations thereof.

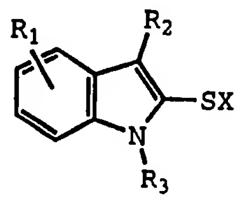
For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water soluble, alkali metal, or alkaline earth metal salts previously enumerated. Such aqueous solution should be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well known to those skilled in the art.

For purposes of topical administration, dilute sterile, aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared in containers suitable for dropwise administration to the eye.

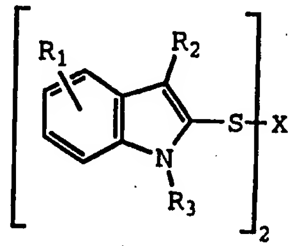
In a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, the weight ratio of carrier to active ingredient will normally be in the range from 1:4 to 4:1, and preferably 1:2 to 2:1. However, in any given case, the ratio chosen will depend on such factors as the solubility of the active component, the dosage contemplated and the precise route of administration.

The following Table 1 sets out physical data for 137 compounds within the general Formula I, representative of it, and preparable by the processes of the invention.

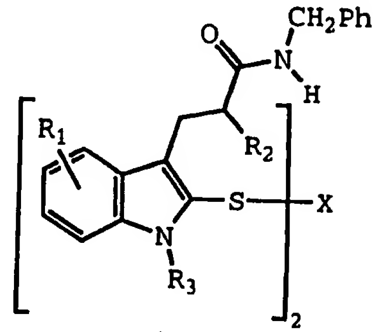
TABLE 1



A



B



B1

No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
1	A	H	CH_2COOH	H	H	166-168	$C_{10}H_9NO_2S$	known[d]
2	A	H	CH_2COOH	Me	H	150-153	$C_{11}H_{11}NO_2S$	known[d]
3	A	H	CH_2COOMe	H	H	150-152	$C_{11}H_{11}NO_2S$	C,H,N,S[e]
4	A	H	CH_2COOMe	Me	H	68-70	$C_{12}H_{13}NO_2S$	C,H,N,S
5	A	H	CH_2COOEt	Me	H	47-48	$C_{13}H_{15}NO_2S$	C,H,N,S[e]
6	A	H	$CH_2CONHCH_2Ph$	H	H	193-195	$C_{17}H_{10}N_2OS$	C,H,N,S
7	A	H	$(CH_2)_2COOH$	H	H	170-173	$C_{11}H_{11}NO_2S$	C,H,N
8	A	H	$(CH_2)_2COOH$	Me	H	126-128.5	$C_{12}H_{13}NO_2S \cdot 0.25H_2O$	C,H,N,S
9	A	H	$(CH_2)_2COOMe$	H	H	95.5-98	$C_{12}H_{13}NO_2S$	C,H,N,S

TABLE 1 (cont'd)

No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
10	A	H	$(CH_2)_2COOEt$	H	H	oil[b]	$C_{13}H_{15}NO_2S$	C,H,N,S
11	A	H	$(CH_2)_2COOMe$	Me	H	71-73	$C_{13}H_{15}NO_2S$	C,H,N,S
12	A	H	$(CH_2)_2COOEt$	Me	H	61-63	$C_{14}H_{17}NO_2S$	C,H,N,S
13	A	H	$(CH_2)_2CONHCH_2Ph$	H	H	149.5-151	$C_{18}H_{18}NO_2S \cdot 0.5H_2O$	C,H,N,S
14	A	H	$(CH_2)_2CONH_2$	H	H	160-163	$C_{11}H_{12}N_2OS$	C,H,N,S
15	A	H	$(CH_2)_3COOH$	H	H	132-134	$C_{12}H_{13}NO_2S$	C,H,N,S
16	A	H	$(CH_2)_3COOH$	Me	H	144-146.5	$C_{13}H_{15}NO_2S \cdot H_2O$	C,H,N,S
17	A	H	$(CH_2)_3COOMe$	H	H	109-110	$C_{13}H_{15}NO_2S$	C,H,N,S
18	A	H	$(CH_2)_3COOMe$	Me	H	103-106	$C_{14}H_{17}NO_2S$	C,H,N,S
19	A	7-aza	CONHPh	Me	H	162-164	$C_{15}H_{13}N_3O_2S \cdot CH_3OH$	C,H,N,S
20	A	5-Cl	CONHPh	Me	H	312-320	$C_{16}H_{13}ClN_2OS$	HRMS
21	A	H	CONHPh	Me	H	149-151	$C_{16}H_{14}N_2OS$	C,H,N,S
22	A	H	CONHPh	Me	Me	116-118	$C_{17}H_{16}N_2OS$	C,H,N,S
23	A	H	CONHPh	Me	CH_2Ph	144-146	$C_{23}H_{20}N_2OS_2$	C,H,N,S
24	A	H	COPh	Me	H	130-132	$C_{16}H_{13}NOS$	C,H,N,S
25	A	H	COPhpCOOH	Me	H	282 (dec)	$C_{17}H_{13}NO_3S \cdot 0.25H_2O$	C,H,N
26	A	H	COPhpCOOMe	Me	H	164-166	$C_{18}H_{15}NO_3S$	C,H,N,S
27	B	H	CH_2COOMe	H	-	160-162	$C_{22}H_{20}N_2O_4S_2$	C,H,N,S[f]
28	B	H	CH_2COOMe	Me	-	130-132.5	$C_{24}H_{24}N_2O_4S_2$	C,H,N,S
29	B	H	CH_2COOH	H	-	196-199	$C_{20}H_{16}N_2O_4S_2$	known[d]
30	B	H	CH_2COOH	H	S	199-202	$C_{20}H_{16}N_2O_4S_3$	C,H,N,S
31	B	H	CH_2COOMe	H	S	130-132	$C_{22}H_{20}N_2O_4S_3$	C,H,N,S[f]
32	B	H	CH_2COOH	Me	-	190-192.5	$C_{22}H_{20}N_2O_4S_2$	known[d]

TABLE 1 (cont'd)

No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
33	B	H	CH_2COOEt	Me	-	117-119	$C_{26}H_{28}N_2O_4S_2$	C,H,N,S
34	B	H	$CH_2CONHCH_2Ph$	H	-	200.5-203.5	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
35	B	H	CH_2CN	H	-	168.5-169.5	$C_{20}H_{14}N_4S_2$ (lit ref)[g]	C,H,N,S
36	B	H	$(CH_2)_2COOH$	H	-	118-120.5	$C_{22}H_{20}N_2O_4S_2 \cdot H_2O$	C,H,N,S
37	B	H	$(CH_2)_2COOH$	Me	-	158.5-160	$C_{24}H_{24}N_2O_4S_2$	C,H,N,S
38	B	H	$(CH_2)_2COOEt$	H	-	137-139	$C_{26}H_{28}N_2O_4S_2$	C,H,N,S
39	B	H	$(CH_2)_2COOMe$	H	-	162.5-164	$C_{24}H_{24}N_2O_4S_2$	C,H,N,S
40	B	H	$(CH_2)_2COOMe$	Me	-	139-141.5	$C_{26}H_{28}N_2O_4S_2$	C,H,N,S
41	B	5-Me	$(CH_2)_2COOH$	H	-	91.5-95	$C_{24}H_{24}N_2O_4S_2$	HRMS[c]
42	B	5-Me	$(CH_2)_2COOEt$	H	-	138.5-139	$C_{28}H_{32}N_2O_4S_2 \cdot 0.5C_6H_6$	C,H,N,S
43	B	6-Me	$(CH_2)_2COOH$	H	-	126-128	$C_{24}H_{24}N_2O_4S_2 \cdot 0.5H_2O$	C,H,N,S
44	B	6-Me	$(CH_2)_2COOEt$	H	-	122-123.5	$C_{28}H_{32}N_2O_4S_2$	C,H,N,S
45	B	7-Me	$(CH_2)_2COOH$	H	-	172.5-175	$C_{24}H_{24}N_2O_4S_2$	C,H,N
46	B	7-Me	$(CH_2)_2COOEt$	H	-	120-122.5	$C_{28}H_{32}N_2O_4S_2$	C,H,N,S
47	B	H	$(CH_2)_2CONHCH_2Ph$	H	-	141-144	$C_{36}H_{34}N_4O_2S_2$	C,H,N,S
48	B	H	$(CH_2)_2CN$	H	-	167-169	$C_{21}H_{16}N_4S_2$ (lit ref)[g]	
49	B	H	$(CH_2)_2NO_2$	H	-	153-154	$C_{20}H_{18}N_4O_4S_2 \cdot 0.5H_2O$	C,H,N,S
50	B	H	$(CH_2)_2CONH_2$	H	-	101 (dec)	$C_{22}H_{22}N_4O_2S_2 \cdot 0.5H_2O$	C,H,N,S
51	B	H	$(CH_2)_2CONHMe$	H	-	162.5-164	$C_{24}H_{26}N_4O_2S_2$	C,H,N,S
52	B	H	$(CH_2)_2CONHOMe$	H	-	176-178	$C_{24}H_{26}N_4O_4S_2$	C,H,N,S
53	B	H	$(CH_2)_2CONMe_2$	H	-	179-180	$C_{26}H_{30}N_4O_2S_2$	C,H,N,S
54	B	H	$(CH_2)_2CONH(CH_2)_2Ph$	H	-	oil	$C_{38}H_{38}N_4O_2S_2$	HRFABMS
55	B	H	$(CH_2)_2CONHCH_2Ph(4\text{-}COOMe)$	H	-	151-153	$C_{40}H_{38}N_4O_6S_2$	C,H,N,S

TABLE 1 (cont'd)

No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
56	B	H	$(CH_2)_2CONHCH_2Ph\{4\text{-}COOH\}$	H	-	135.5-138.5 (dec)	$C_{38}H_{34}N_4O_6S_2 \cdot H_2O$	C,H,N,S
57	B	H	$(CH_2)_2CONHCH_2Ph\{3\text{-}OH, 4\text{-}COOMe\}$	H	-	183-185	$C_{40}H_{38}N_4O_8S_2$	C,H,N,S
58	B	H	$(CH_2)_2CONHCH_2Ph\{3\text{-}OH, 4\text{-}COOH\}$	H	-	160-163.5 (dec)	$C_{38}H_{34}N_4O_8S_2 \cdot H_2O$	C,H,N,S
59	B	H	$(CH_2)_2CONHPh$	H	-	114 (dec)	$C_{34}H_{30}N_4O_2S_2 \cdot 0.5H_2O$	C,H,N,S
60	B1	H	NHAc	H	-	140-144# (dec)	$C_{40}H_{40}N_6O_4S_2 \cdot 0.5H_2O$	C,H,N,S
					-	154.5-157.5# (dec)	$C_{40}H_{40}N_6O_4S_2$	C,H,N,S
61	B1	H	$NHCOCF_3$	H	-	160-164 (dec)	$C_{40}H_{34}F_6N_6O_4S_2 \cdot 0.5H_2O$	C,H,N,S
62	B1	H	NH_2	H	-	147-150 (dec)	$C_{36}H_{36}N_6O_2S_2 \cdot 0.5H_2O$	C,H,N,S
63	B1	H	OAc	H	-	120-124 (dec)	$C_{40}H_{34}N_4O_6S_2$	C,H,N,S
64	B1	H	OH	H	-	120-125	$C_{36}H_{34}N_4O_4S_2$	C,H,N,S
65	B	H	$(CH_2)_3COOH$	H	-	141-143.5	$C_{24}H_{24}N_2O_4S_2 \cdot 0.5H_2O$	C,H,N,S
66	B	H	$(CH_2)_3COOH$	Me	-	106.5-109.5	$C_{26}H_{28}N_2O_4S_2 \cdot 2AcOH$	C,H,N,S
67	B	H	$(CH_2)_3COOMe$	H	-	91-93	$C_{26}H_{28}N_2O_4S_2$	C,H,N,S
68	B	H	$(CH_2)_3COOMe$	Me	-	112-113	$C_{28}H_{32}N_2O_4S_2$	C,H,N,S
69	B	H	$(CH_2)_3CONHCH_2Ph$	H	-	98.5-101	$C_{38}H_{38}N_4O_2S_2$	C,H,N,S
70	B	H	CONHPh	Me	-	187-188	$C_{32}H_{26}N_4O_2S_2$	C,H,N,S
71	B	H	CONHPh	Et	-	200-202	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
72	B	4-Cl	CONHPh	Me	-	225-228	$C_{32}H_{24}Cl_2N_4O_2S_2$	C,H,N,Cl
73	B	5-Cl	CONHPh	Me	-	214-216	$C_{32}H_{24}Cl_2N_4O_2S_2$	C,H,N,S
74	B	7-Cl	CONHPh	Me	-	232-234	$C_{32}H_{24}Cl_2N_4O_2S_2$	C,H,N,Cl
75	B	4-Me	CONHPh	Me	-	237-239	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
76	B	5-Me	CONHPh	Me	-	231-234	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S

TABLE 1 (cont'd)

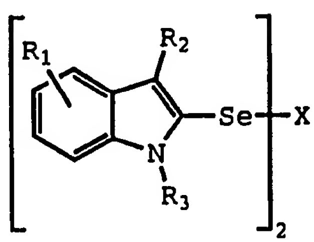
No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
77	B	6-Me	CONHPh	Me	-	192-195	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
78	B	7-Me	CONHPh	Me	-	221-223	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
79	B	4-OMe	CONHPh	Me	-	225-228	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
80	B	5-OMe	CONHPh	Me	-	161-164	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
81	B	6-OMe	CONHPh	Me	-	197-200	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
82	B	7-OMe	CONHPh	Me	-	205-206	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
83	B	7-aza	CONHPh	Me	-	197-198	$C_{30}H_{24}N_6O_2S_2$	C,H,N,S
84	B	5-CF_3	CONHPh	Me	-	214-216	$C_{34}H_{24}F_6N_4O_2S_2$	C,H,N,S
85	B	6-Cl	CONHPh	Me	-	243-245	$C_{32}H_{24}Cl_2N_4O_2S_2$	C,H,N,S
86	B	5-NO_2	CONHPh	Me	-	236-240	$C_{32}H_{24}N_6O_6S_2 \cdot 2H_2O$	C,H,N
87	B	5-F	CONHPh	Me	-	205-207	$C_{32}H_{24}F_2N_4O_2S_2$	C,H,N,S
88	B	5-CN	CONHPh	Me	-	221-224	$C_{34}H_{24}N_6O_2S_2 \cdot 0.5H_2O$	C,H,N,S
89	B	5-Br	CONHPh	Me	-	219-221	$C_{32}H_{24}Br_2N_4O_2S_2$	C,H,N,S
90	B	4-OAc	CONHPh	Me	-	194	$C_{36}H_{30}N_4O_6S_2$	HRFABMS
91	B	5-OAc	CONHPh	Me	-	147-150	$C_{36}H_{30}N_4O_6S_2 \cdot 0.5H_2O$	C,H,N,S
92	B	5-OH	CONHPh	Me	-	185-187	$C_{32}H_{26}N_4O_4S_2 \cdot H_2O$	C,H,N
93	B	6-OAc	CONHPh	Me	-	219-222	$C_{36}H_{30}N_4O_6S_2$	C,H,N,S
94	B	6-OH	CONHPh	Me	-	185-187	$C_{32}H_{26}N_4O_4S_2$	HRMS
95	B	7-OAc	CONHPh	Me	-	212-214	$C_{36}H_{30}N_4O_6S_2 \cdot 0.5H_2O$	C,H,N,S
96	B	7-OH	CONHPh	Me	-	206-207	$C_{32}H_{26}N_4O_4S_2$	C,H,N,S
97	B	H	CONHMe	Me	-	162-165	$C_{22}H_{22}N_4O_2S_2$	HRMS[c]
98	B	H	$CONHCH_2Ph$	Me	-	145-147	$C_{34}H_{30}N_4O_2S_2$	C,H,N,S
99	B	H	SO_2Php-Me	H	-	230-233	$C_{30}H_{24}N_2O_4S_4$	C,H,N,S
100	B	H	COPh	Me	-	199-202	$C_{32}H_{24}N_2S_2O_2$	C,H,N,S

TABLE 1 (cont'd)

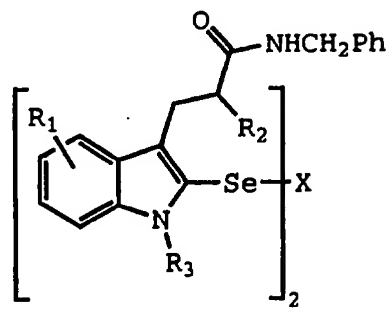
No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
101	B	H	COPhpCOOH	Me	-	241-246	$C_{34}H_{24}N_2S_2O_6 \cdot 1.5H_2O$	C,H
102	B	H	COPhpCOOMe	Me	-	200-203	$C_{36}H_{28}N_2O_6S_2$	C,H,N,S
103	B	H	Me	Me	-	113-115	$C_{20}H_{20}N_2S_2$	C,H,N,S
104	B	H	CONHPh{4-COOMe}	Me	-	184-186	$C_{36}H_{30}N_4O_6S_2 \cdot H_2O$	C,H,N,S
105	B	H	CONHPh{4-COOH}	Me	-	221	$C_{34}H_{26}N_4O_6S_2 \cdot 0.5H_2O$	C,H,N,S
106	B	H	CONHPh{3-COOMe}	Me	-	193-195	$C_{36}H_{30}N_4O_6S_2$	C,H,N,S
107	B	H	CONHPh{3-COOH}	Me	-	219-220	$C_{34}H_{26}N_4O_6S_2$	C,H,N,S
108	B	H	CONHPh{2-COOMe}	Me	-	179-181	$C_{36}H_{30}N_4O_6S_2$	C,H,N,S
109	B	H	CONHPh{2-COOH}	Me	-	184-186	$C_{34}H_{26}N_4O_6S_2$	C,H,N,S
110	B	H	$CONHCH_2Ph${4-COOMe}	Me	-	178-180	$C_{38}H_{34}N_4O_6S_2$	C,H,N,S
111	B	H	$CONHCH_2Ph${4-COOH}	Me	-	178-180	$C_{36}H_{30}N_4O_6S_2 \cdot 1.5H_2O$	C,H,N,S
112	B	H	$CONHCH_2COOH$	Me	-	196-198	$C_{24}H_{22}N_4O_6S_2$	C,H,N,S
113	B	H	CON(Me)Ph	Me	-	158-163	$C_{34}H_{31}N_4S_2O_2$	C,H,N,S
114	B	H	$CONHCH_2CH(OH)CH_2OH$	Me	-	198	$C_{26}H_{30}N_4O_6S_2$	C,H,N,S
115	B	H	$CONHCH_2CH_2NMe_2$	Me	-	163.5-165	$C_{28}H_{36}N_6O_2S_2$	C,H,N,S
116	B	H	CONH-4-pyridyl	Me	-	226-229	$C_{30}H_{24}N_6O_2S_2$	C,H,N,S
117	B	H	CONH-3-pyridyl	Me	-	257-260	$C_{30}H_{24}N_6O_2S_2$	C,H,N,S
118	B	H	$CONH_2$	Me	-	186-188	$C_{20}H_{18}N_4O_2S_2 \cdot 0.5H_2O$	C,H,N,S
119	B	H	$CONMe_2$	Me	-	96-102	$C_{24}H_{26}N_4O_2S_2 \cdot 0.5H_2O$	C,H,N
120	B	H	CN	Me	-	205-207	$C_{20}H_{14}N_4S_2$	C,H,N,S
121	B	H	COMe	Me	-	178.5-179.5	$C_{22}H_{20}N_2O_2S_2 \cdot 0.5H_2O$	C,H,N,S
122	B	H	CONH-2-pyridyl	Me	-	270-272	$C_{30}H_{24}N_6O_2S_2 \cdot 0.25H_2O$	C,H,N,S
123	B	H	CONH-furyl	Me	-	175-176	$C_{28}H_{20}N_2O_4S_2$	
124	B	H	CONH-thienyl	Me	-	183 (DEC)	$C_{28}H_{22}N_4O_4S_2 \cdot 0.5H_2O$	C,H,N

TABLE 1 (cont'd)

No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
125	B	H	$CONHCH_2Ph$	H	-	203-205	$C_{32}H_{26}N_4O_2S_2$	C,H,N,S
126	B	H	CONHPh	H	-	220-222.5	$C_{30}H_{22}N_4O_2S_2$	C,H,N,S
127	B	H	CONHMe	H	-	232-236	$C_{20}H_{18}N_4O_2S_2$	C,H,N,S
128	B	H	CONHPh	$(CH_2)_3NMe_2$	-	165	$C_{28}H_{36}N_6O_2S_2$	C,H,N,S



D



D1

129	D	H	COOt-Bu	CH_3	-	187-189	$C_{28}H_{32}N_2O_4Se_2 \cdot 0.2H_2O$	C,H,N
130	D	H	COOH	CH_3	-	174 (dec)	$C_{20}H_{16}N_2O_4Se_2 \cdot 0.1H_2O$	C,H,N
131	D	H	CONHMe	CH_3	-	225-230 (dec)	$C_{22}H_{22}N_4O_2Se_2 \cdot 0.9H_2O$	C,H,N
132	D	H	$CONH(CH_2)_2NEt_2$	CH_3	-	160-164	$C_{32}H_{44}N_6O_2Se_2 \cdot 2.0HCl \cdot 1.7H_2O$	C,H,N,Cl^-

TABLE 1 (cont'd)

No.	Formula	R_1	R_2	R_3	X	mp (°C)	Molecular Formula	Analysis[a]
133	D	H	$CONHCH_3$	H	-	272-275	$C_{20}H_{18}N_4O_2Se_2 \cdot 0.9H_2O$	C,H,N
134	D	H	$CONH(CH_2)_2NEt_2$	H	-	257-259 (dec)	$C_{30}H_{40}N_6O_2Se_2 \cdot 2.0HCl \cdot H_2O$	C,H,N
135	D	H	$CONHCH_3$	$(CH_2)_2NEt_2$	-	156-157	$C_{32}H_{44}N_6O_2Se_2 \cdot 0.5H_2O$	C,H,N
136	D1	H	NH_2[R-(R*,R*)]	H	-	172-174	$C_{36}H_{36}N_6O_2Se_2 \cdot 1.5H_2O$	C,H,N
137	D1	H	NH_2[S-(R*,R*)]	H	-	171 (dec)		

Diastereomers
[a] Analyses for all listed elements within ±0.4%
[b] Noncrystalline
[c] High-resolution mass spectrum molecular ion
[d] Wieland T, Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146
[e] Takase S, Uchida I, Tanaka H, Aoki H, Tetrahedron 1986;42:5879
[f] Palmisano G, Brenna E, Danieli B, Lesma G, Vodopivec B, Fiori G, Tet. Lett. 1990;31:7229
[g] Piotrowska H, Serafin B, Wejroch-Matacz K, Rocz. Chem. 1975;49:635-638.

EXAMPLES

The invention and the best mode for practicing the same are illustrated by the following Examples A-K.

EXAMPLE A

Preparation of Compounds 15, 17, 65, and 46 of Table 1 by the Method Outlined in Scheme 1

Concentrated HCl (16.6 mL) was added dropwise with stirring, over 10 minutes, to a solution of 4-(3-indolyl)butanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (2.00 g) in DMSO (7.0 mL) at room temperature (method of Savige WE, Fontana A, J. Chem. Soc. Chem. Commun. 1976:599). After 15 minutes reaction, the mixture was diluted with water (80 mL) and extracted with EtOAc (4 x 100 mL). Removal of the solvent gave crude 4-(2-oxo-3-indolinyl)butanoic acid [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (2.07 g, 96%) as a green-brown solid; mp (water) 169-171°C (Hinman RL, Bauman CP, J. Org. Chem. 1964;29:1206 record mp 170-171°C).

Acetyl chloride (10 mL) was added dropwise with stirring to an ice-cooled solution of the above crude acid [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (2.05 g) in dry MeOH (50 mL), and the mixture stirred at 20°C for 18 hours. The solvent was removed, and repeated evaporation from MeOH yielded a brown oil, which was dissolved in $CHCl_3$ (100 mL) and washed with water (2 x 100 mL). Removal of the solvent gave crude methyl 4-(2-oxo-3-indolinyl)butanoate [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (2.20 g) as an oil. A pure sample was obtained by chromatography on silica gel and elution with EtOAc/light petroleum (1:2) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ 8.82 (1H, s, NH), 7.24 (1H, d, J = 7.7 Hz, ArH), 7.21 (1H, t, J = 7.8 Hz, ArH), 7.03 (1H, td, J = 7.6, 0.8 Hz, ArH), 6.91 (1H, d, J = 7.7 Hz, ArH), 3.65 (3H, s, $COOCH_3$), 3.49 (1H, t, J = 6.0 Hz, H-3), 2.34 (2H, t, J = 7.5 Hz, CH_2CO), 2.00, 1.72 (4H, 2xm, 3-CH_2CH_2).

^{13}C NMR ($CDCl^3$): δ 180.23 (s, CONH), 173.57 (s, $\underline{C}OOCH_3$), 141.54, 129.24 (2xs, Ar), 127.97, 124.11, 122.37, 109.80 (4xd, Ar), 51.53 (q, $COO\underline{C}H_3$), 45.74 (d, C3), 33.83, 29.79, 21.18 (3xt, $(\underline{C}H_3)_3CO$).

Analysis calculated for $C_{13}H_{15}NO_3 \cdot H_2O$ requires:

C, 6.45; H, 6.7; N, 5.6%.

Found: C, 64.4; H, 6.5; N, 5.7%.

A solution of the above crude ester [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (0.48 g) in dry dioxane (10 mL) was treated with P_2S_5 (0.26 g) and $NaHCO_3$ (0.36 g), then the mixture was stirred under nitrogen at 95°C for 1 hour. The resulting solution was concentrated under reduced pressure, and the residue was diluted with CH_2Cl_2 (100 mL) and filtered. The filtrate was washed with water, solvent was removed, and the residue (0.55 g) was chromatographed on silica gel (elution with CH_2Cl_2) to give crude methyl 4-(2-thioxo-3-indolinyl)butanoate [IV: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (17) (0.18 g, 35%); mp (benzene-light petroleum) 109-110°C.

^{1}N NMR ($CDCl_3$): δ 10.59 (1H, s, NH), 7.31 (1H, d, J = 7.4 Hz, ArH), 7.27 (1H, td, J = 7.7, 0.9 Hz, ArH), 7.14 (1H, td, J = 7.5, 0.9 Hz, ArH), 7.02 (1H, d, J = 7.7 Hz, ArH), 3.85 (1H, t, J = 5.5 Hz, H-3), 3.64 (3H, s, $COOCH_3$), 2.32 (2H, t, J = 7.5 Hz, CH_2CO), 2.26, 2.15, 1.67, 1.46 (4H, 4xm, 3-CH_2CH_2).

^{13}C NMR ($CDCl_3$): δ 207.80 (s, CSNH), 173.69 (s, $\underline{C}OOCH_3$), 143.27, 133.85 (2xs, ArH), 128.19, 124.17,

124.02, 110.12 (4xd, ArH), 57.36 (d, C-3), 51.61 (q, $COO\underline{C}\underline{H}_3$), 33.92, 32.76, 20.41 (3xt, $(\underline{C}\underline{H}_2)_3CO$).
Analysis calculated for $C_{13}N_{15}NO_2S$ requires:
C, 62.6; H, 6.1; N, 5.6; S, 12.9%.
Found: C, 62.8; H, 5.9; N, 5.7; S, 12.9%.

A solution of **17** (0.39 g) in MeOH was exposed to air for 13 days, then the solvent was removed. Chromatography of the residue on silica gel (elution with CH_2Cl_2) yielded bis[methylindolyl-3-butanoate-(2)]-disulfide [V: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (**67**) (0.31 g, 80%); mp (MeOH-dilute HCl) 91-93°C.
^1N NMR ($CDCl_3$): δ 8.19 (1H, s, NH), 7.57 (1H, d, J = 7.9 Hz, ArH), 7.28 (1H, d, J = 8.0 Hz, ArH), 7.24 (1H, ddd, J = 8.2, 7.1, 1.1 Hz, ArH), 7.12 (1H, ddd, J = 8.0, 6.9, 1.4 Hz, ArH), 3.56 (3H, s, $COOCH_3$), 2.67, 2.18 (2x2H, 2xt, J = 7.4 Hz, $C\underline{H}_2CH_2C\underline{H}_2CO$), 1.85 (2H, quin, J = 7.4 Hz, $CH_2C\underline{H}_2CH_2CO$).
^{13}C NMR ($CDCl_3$): δ 174.02 (s, $\underline{C}OOCH_3$), 137.29, 127.49, 125.99 (3xs, ArH), 124.21 (d, ArH), 123.70 (s, ArH), 119.95, 119.88, 111.08 (3xd, ArH), 51.42 (q, $COO\underline{C}H_3$), 33.45, 25.67, 23.95 (3xt, $(\underline{C}H_2)_3CO$).
Analysis calculated for $C_{26}H_{28}N_2O_4S_2$ requires:
C, 62.9; H, 5.7; N, 5.7; S, 12.9%.
Found: C, 62.6; H, 6.0; N, 5.5; S, 13.1%.

A mixture of **17** (0.26 g) in MeOH (10 mL) and K_2CO_3 (0.55 g) in water (3 mL) was stirred at room temperature for 2 days. $NaBH_4$ (100 mg) was then added, and the mixture stirred for 25 minutes, then diluted with water (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The aqueous portion was acidified (to pH 3) with dilute HCl and extracted with EtOAc (3 x 100 mL). This extract was concentrated under reduced pressure, and the residue was crystallized from CH_2Cl_2-light petroleum to give 4-(2-thioxo-

3-indolinyl)butanoic acid [IV: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (15) (30 mg, 12%); mp 132-134°C.
^1H NMR (CD_3OD): δ 7.34 (1H, d, J = 7.4 Hz, ArH), 7.26 (1H, td, J = 7.7, 1.1 Hz, ArH), 7.12 (1H, td, J = 7.5, 0.8 Hz, ArH), 7.00 (1H, d, J = 7.8 Hz, ArH), 2.25 (2H, t, J = 7.5 Hz, C$\underline{H}_2$COOH), 2.24, 2.10, 1.55, 1.33 (4H, 4xm, 3-CH_2CH).
Analysis calculated for $C_{12}H_{13}NO_2S$ requires:
C, 61.3; H, 5.6; N, 6.0; S, 13.6%
Found: C, 61.1; H, 6.2; N, 6.1; S, 13.5%.

Similar hydrolysis of 67 (at 30°C for 6 hours, then 20°C for 1 day) gave bis[indolyl-3-butanoic acid-(2)]disulfide [V: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (65) (30 mg, 20%); mp (aqueous MeOH) 141-143.5°C.
^1H NMR (CD_3OD): δ 7.48 (1H, dt, J = 8.0, 0.8 Hz, ArH), 7.32 (1H, dt, J = 8.2, 0.7 Hz, ArH), 7.16 (1H, ddd, J = 8.1, 7.1, 1.1 Hz, ArH), 7.00 (1H, ddd, J = 8.0, 7.1, 0.8 Hz, ArH), 2.42 (2H, t, J = 7.6 Hz, CH_2CO), 1.93 (2H, t, J = 7.3 Hz, 3-CH_2), 1.58 (2H, quin, J = 7.5 Hz, $CH_2C\underline{H}_2CH_2CO$).
^{13}C NMR (CD_3OD): δ 177.52 (s, COOH), 139.31, 128.69, 126.69, 124.84 (4xs, ArH), 124.67, 120.48, 120.27, 112.34 (4xd, ArH), 34.39, 27.24, 24.82 (3xt, $(\underline{C}H_2)_3COOH$).
Analysis calculated for $C_{24}H_{24}N_2O_4S_2 \cdot H_2O$ requires:
C, 60.4; H, 5.2; N, 5.9; S, 13.4%.
Found: C, 60.4; H, 5.4; N, 5.9; S, 13.6%.

<u>Compounds 7, 9, 36 and 39 of Table 1</u>

Similar treatment of methyl 3-(3-indolinyl)-propanoic [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (0.93 g) with DMSO/HCl, followed by esterification with diazomethane and chromatography on silica gel, gave methyl 3-(2-oxo-3-indolyl)propanoate [III: R_1-R_3 = H,

R_2 = $(CH_2)_2COOMe$] (0.89 g, 89%) as a yellow oil (Julian PL, Printy HC, J. Am. Chem. Soc. 1953;75:5301-5305 report mp 79-80°C).
^1H NMR ($CDCl_3$): δ 8.75 (1H, s, NH), 7.22 (2H, m, ArH), 7.03 (1H, ddd, J = 7.8, 7.1, 1.1 Hz, ArH), 6.91 (1H, dd, J = 7.3, 1.3 Hz, ArH), 3.63 (3H, s, OCH_3), 3.54 (1H, t, J = 5.8 Hz, H-3), 2.61-2.20 (4H, m, 3-CH_2CH_2).
Analysis calculated for $C_{12}H_{13}NO_3$ requires:
M+ 219.0895.
HREIMS m/z Found: M+ 219.0898.

Treatment of this ester [III: R_1 = R_3 = H, R_2 = $(CH_2)_2COOMe$] (0.89 g) with P_2S_5 as above, followed by chromatography on silica gel, eluting with EtOAc/light petroleum (3:1), gave an oil (0.44 g). Crystallization from MeOH gave 2,2'-dithiobis[methyl 3-(3-indolyl)propanoate [V: R_1 = R_3 = H, R_2 = $(CH_2)_2COOMe$] (39) (61 mg, 6%); mp 162.5-164°C.
^1H NMR ($CDCl_3$): δ 8.21 (1H, s, NH), 7.55 (1H, dd, J = 8.0, 0.7 Hz, ArH), 7.25 (2H, m, ArH), 7.12 (1H, ddd, J = 8.0, 5.4, 2.6 Hz, ArH), 3.56 (3H, s, OCH_3), 2.98, 2.47 (2x2H, 2xt, J = 7.9 Hz, 3-CH_2CH_2).
^{13}C NMR ($CDCl_3$): δ 173.38 (s, $COOCH_3$), 137.25, 127.21, 125.80 (3xs, Ar), 124.30 (d, Ar), 122.79 (s, Ar), 120.10, 119.59, 111.21 (3xd, Ar), 51.56 (q, OCH_3), 34.97 (t, CH_2CO), 20.27 (t, 3-CH_2).
Analysis calculated for $C_{24}H_{24}N_2O_4S_2$ requires:
C, 61.5; H, 5.2; N, 6.0; S, 13.7%.
Found: C, 61.4; H, 5.3; N, 6.1; S, 13.7%.

Crystallization of the mother liquor residue from benzene/light petroleum gave methyl 3-(2-thioxo-3-indolinyl)propanoate [IV: R_1 = R_3 = H, R_2 = $(CH_2)_2COOMe$] (9) (0.24 g, 25%); mp (CH_2Cl_2/light petroleum) 96-98°C.

^1H NMR ($CDCl_3$): δ 9.83 (1H, s, NH), 7.29 (2H, m, ArH), 7.16 (1H, td, *J* = 7.5, 0.9 Hz, ArH), 6.99 (1H, d, *J* = 7.8 Hz, ArH), 3.91 (1H, t, *J* = 5.4 Hz, H-3), 3.60 (3H, s, OCH_3), 2.52 (2H, m, 3-CH_2), 2.42, 2.11 (2x1H, 2xm, CH_2CO).

^{13}C NMR ($CDCl_3$): δ 207.26 (s, CSNH), 173.37 (s, *C*$OOCH_3$), 143.24, 133.08 (2xs, Ar), 128.43, 124.35, 124.09, 110.01 (4xd, Ar), 56.45 (d, C-3), 51.68 (q, OCH_3), 29.33, 28.19 (2xt, 3-CH_2CH_2).

Analysis calculated for $C_{12}H_{13}NO_2S$ requires:

C, 61.3; H, 5.6; N, 6.0; S, 13.6%.

Found: C, 61.4; H, 5.5; N, 6.0; S, 13.7%.

Hydrolysis of 9 with K_2CO_3/MeOH/H_2O as described above, followed by chromatography on silica gel, reduction with $NaBH_4$ and crystallization from CH_2Cl_2/isopropyl ether/light petroleum gave 3-(2-thioxo-3-indolinyl)propanoic acid [IV: R_1 = R_3 = H, R_2 = $(CH_2)_2COOH$] (7) (25 mg, 22%); mp 170-173°C.

^1H NMR (CD_3COCD_3): δ 11.48 (1H, s, NH), 7.43 (1H, d, J = 7.4 Hz, ArH), 7.30 (1H, t, J = 7.7 Hz, ArH), 7.15 (1H, t, J = 7.4 Hz, ArH), 7.11 (1H, d, J = 7.8 Hz, ArH), 3.90 (1H, t, J = 5.3 Hz, H-3), 2.49 (1H, m, CH_2CH_2CO), 2.37 (2H, m, CH_2CH_2CO), 2.11 (1H, m, CH_2CH_2CO).

^{13}C NMR (CD_3COCD_3): δ 208.48 (s, CSNH), 174.14 (s, COOH), 145.18, 134.55 (2xs, Ar), 129.05, 125.08, 124.30, 110.87 (4xd, Ar), 57.18 (d, C-3), 29,86, 29.25 (2xt, $\underline{C}H_2\underline{C}H_2COOH$).

Analysis calculated for $C_{11}H_{11}NO_2S$ requires:

C, 59.71; H, 5.01; N, 6.33%.

Found: C, 59.49; H, 4.97; N, 6.15%.

Aerial oxidation of 7 in MeOH at 20°C for 12 days, followed by dilution with water, gave

bis[indolyl-3-propanoic acid-(2)]disulfide [V: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (36) (30 mg, 30%); mp (aqueous MeOH) 118-120.5°C.

^{1}H NMR (CD_3OD): δ 7.47 (1H, dt, J = 8.0, 0.8 Hz, ArH), 7.30 (1H, dt, J = 8.1, 0.8 Hz, ArH), 7.15 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.00 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 2.74, 2.2 (2x2H, 2xt, J = 8.0 Hz, $(C\underline{H}_2)_2COOH$).

^{13}C NMR (CD_3OD): δ 176.95 (s, COOH), 139.26, 128.26 126.65 (3xs, Ar), 124.69 (d, Ar), 123.66 (s, Ar), 120.36, 120.20, 112.41 (3xd, Ar), 36.29, 21.22 (2xt, $(\underline{C}H_2)_2COOH$).

Analysis calculated for $C_{22}H_{20}N_2O_4S_2 \cdot H_2O$ requires:
C, 57.6; H, 4.8; N, 6.1; S, 14.0%.
Found: C, 57.6; H, 5.0; N, 6.1; S, 13.9%.

<u>Compounds 3 and 27 of Table 1</u>

Similar reaction of methyl 2-(2-oxo-3-indolinyl)-acetate [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$: Takase S, Uchida I, Tanaka H, Aoki H, <u>Tetrahedron</u> 1986;42:5879] (0.13 g) with P_2S_5 gave methyl 2-(2-thioxo-3-indolinyl)acetate [IV: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (3) (50 mg, 36%); mp (MeOH) 150-152°C.

^{1}N NMR ($CDCl_3$): δ 10.36 (1H, s, NH), 7.29 (1H, d, J = 7.6 Hz, ArH), 7.27 (1H, t, J = 7.8 Hz, ArH), 7.11 (1H, t, J = 7.6 Hz, ArH), 7.00 (1H, d, J = 7.8 Hz, ArH), 4.14 (1H, dd, J = 8.4, 4.2 Hz, H-3), 3.72 (3H, s, $COOCH_3$), 3.35 (1H, dd, J = 17.0, 4.2 Hz, CH_2CO), 2.88 (1H, dd, J = 17.0, 8.5 Hz, CH_2CO).

^{13}C NMR ($CDCl_3$): δ 206.59 (s, CSNH), 171.53 (s, $\underline{C}OOCH_3$), 143.10, 133.53 (2xs, ArH), 128.45, 124.20, 124.12, 110.07 (4xd, ArH), 53.53 (d, C3), 52.02 (q, $COO\underline{C}H_3$), 37.94 (t, CH_2).

Analysis calculated for $C_{11}H_{11}NO_2S$ requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.9; H, 5.3; N, 6.4; S, 14.4%.

A solution of **3** (0.10 g) in benzene-light petroleum (1:1, 30 mL) exposed to air for 2 days gave a quantitative yield of bis[methylindolyl-3-acetate-(2)]-disulfide [V: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (Compound **27** of Table I); mp (benzene/light petroleum) 160-162°C.

^{1}N NMR ($CDCl_3$): δ 8.69 (1H, s, NH), 7.52 (1H, dd, J = 8.2, 0.6 Hz, ArH), 7.21 (1H, ddd, J = 8.2, 6.6, 1.1 Hz, ArH), 7.12 (2H, m, ArH), 3.83 (2H, s, CH_2CO), 3.71 (3H, s, $COOCH_3$).

^{13}C NMR ($CDCl_3$): δ 172.54 (s, $\underline{C}OOCH_3$), 137.20, 127.19, 127.03 (3xs, ArH), 124.26, 120.31, 119.45 (3xd, ArH), 116.23 (s, ArH), 111.41 (d, ArH), 52.25 (q, OCH_3), 30.51 (t, $\underline{C}H_2CO$).

Analysis calculated for $C_{22}H_{20}N_2O_4S_2$ requires:

C, 60.0; H, 4.6; N, 6.4; S, 14.6%.

Found: C, 60.0; H, 4.8; N, 6.3; S, 14.4%.

Additional amounts of **27** were also obtained from the mother liquors of the P_2S_5 reaction.

<u>Compounds 8, 11, 37, and 40 of Table 1</u>

A solution of 18-crown-6 (0.44 g), potassium t-butoxide (2.20 g) and methyl 3-(3-indolyl)propanoate [II: $R_1 = R_3 = H$; $R_2 = (CH_2)_2COOMe$] (3.24 g) in dry benzene (20 mL) was stirred at 20°C for 15 minutes, then cooled in ice. A solution of CH_3I (3.42 g) in benzene (10 mL) was added, then the flask was sealed and the mixture stirred at 20°C for 1 day (method of Guida WC, Mathre DJ, <u>J. Org. Chem.</u> 1980;45:3172). The resulting solution was filtered to remove salts, washing with CH_2Cl_2, then the combined filtrates washed

with water and the solvents removed. Chromatography on silica gel, eluting with CH_2Cl_2/light petroleum (1:1), gave methyl 3-(1-methyl-3-indolyl)propanoate [II: R_1 = H; R_3 = Me; R_2 = $(CH_2)_2COOMe$] (1.90 g, 52%) as a colorless oil (Snyder HR, Eliel EL, J. Am. Chem. Soc. 1949;71:663-669 report oil, $bp_{0.25}$ 180-190°C).
^1H NMR ($CDCl_3$): δ 7.58 (1H, dt, J = 7.7, 0.9 Hz, ArH), 7.28 (1H, dt, J = 7.9, 1.3 Hz, ArH), 7.21 (1H, ddd, J = 8.1, 6.7, 1.3 Hz, ArH), 7.10 (1H, ddd, J = 7.9, 6.5, 1.5 Hz, ArH), 6.86 (1H, s, H-2), 3.73, 3.67 (2x3H, 2xs, NCH_3, OCH_3), 3.09, 2.70 (2x2H, 2xt, J = 7.6 Hz, 3-CH_2CH_2).
Analysis calculated for $C_{13}H_{15}NO_2$ requires:
M+ 217.1103.
HREIMS *m/z* Found: M+ 217.1101.

Oxidation of the ester [II: R_1 = H; R_3 = Me; R_2 = $(CH_2)_2COOMe$] (1.85 g) with DMSO/HCl as above for 3 hours gave crude 3-(1-methyl-2-oxo-3-indolinyl)-propanoic acid [III: R_1 = H; R_2 = Me; R_3 = $(CH_2)_2COOH$] (2.08 g) as a colorless oil.
^1H NMR (CD_3OD): δ 7.31 (2H, m, ArH), 7.09 (1H, td, J = 8.0, 1.0 Hz, ArH), 6.98 (1H, d, J = 7.6 Hz, ArH), 3.56 (1H, t, J = 6.1 Hz, H-3), 3.20 (3H, s, NCH_3), 2.41-2.15 (4H, m, 3-CH_2CH_2).
^{13}C NMR (CD_3OD): δ 179.64 (s, COOH), 176.55 (s, $CONCH_3$), 145.52, 129.73 (2xs, Ar), 129.39, 125.00, 123.93, 109.64 (4xd, Ar), 45.79 (d, C-3), 31.01, 26.91 (2xt, 3-CH_2CH_2), 26.44 (q, NCH_3).
Analysis calculated for $C_{12}H_{13}NO_3$ requires:
M+ 219.0895.
HREIMS *m/z* Found: M+ 219.0897.

This was esterified with diazomethane as above, then the product chromatographed on silica gel. Elution with EtOAc/light petroleum (1:2) gave methyl

3-(1-methyl-2-oxo-3-indolinyl)propanoate [III: R_1 = H; R_2 = Me; R_3 = $(CH_2)_2COOMe$] (1.40 g, 70%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 7.27 (2H, m, ArH), 7.06 (1H, td, J = 7.5, 0.8 Hz, ArH), 6.83 (1H, d, J = 7.7 Hz, ArH), 3.62 (3H, s, OCH_3), 3.50 (1H, t, J = 6.0 Hz, H-3), 3.20 (3H, s, NCH_3), 2.52-2.18 (4H, m, CH_2CH_2).

^{13}C NMR ($CDCl_3$): δ 177 23 (s, $CONCH_3$), 173.38 (s, $COOCH_3$), 144.36 (s, Ar), 128.20 (d, Ar), 128.11 (s, Ar), 123.92, 122.48, 108.06 (3xd, Ar), 51.64 (q, OCH_3), 44.36 (d, C-3), 30.12 (t, CH_2OCO), 26.14 (q, NCH_3), 25.64 (t, 3-CH_2).

Analysis calculated for $C_{13}H_{15}NO_3$ requires:

M+ 233.1052.

HREIMS *m/z* Found: M+ 233.1055.

Treatment of this ester [III: R_1 = H; R_2 = Me; R_3 = $(CH_2)_2COOMe$] (1.38 g) with P_2S_5 as above followed by chromatography on silica gel, eluting with CH_2CH_2/light petroleum (3:2), gave methyl 3-(1-methyl-2-thioxo-3-indolinyl)propanoate [IV: R_1 = H; R_3 = Me; R_2 = $(CH_2)_2COOMe$] (11) (1.40 g, 95%); mp (benzene/light petroleum) 71-73°C.

^{1}H NMR ($CDCl_3$): δ 7.35 (2H, m, ArH), 7.19 (1H, td, J = 7.5, 0.9 Hz, ArH), 7.00 (1H, d, J = 7.7 Hz, ArH), 3.92 (1H, t, J = 5.4 Hz, H-3), 3.63, 3.58 (2x3H, 2xs, NCH_3, OCH_3), 2.53 (2H, m, 3-CH_2), 2.34, 2.03 (2x1H, 2xm, CH_2CO).

^{13}C NMR ($CDCl_3$): δ 204.77 (s, $CSNCH_3$), 173.32 (s, $COOCH_3$), 145.89, 132.37 (2xs, Ar), 128.40, 124.31, 123.99, 109.51 (4xd, Ar), 56.26 (d, C-3), 51.61 (q, OCH_3), 31.35 (q, NCH_3), 29.31, 28.46 (2xt, 3-CH_2CH_2).

Analysis calculated for $C_{13}H_{15}NO_2S$ requires:

C, 62.6; H, 6.1; N, 5.6; S, 12.9%.

Found: C, 62.7; H, 6.3; N, 5.7; S, 13.0%.

Oxidation of (11) (0.70 g) with $FeCl_3$ (0.70 g) in $EtOAc/CH_2Cl_2$, chromatography of the product on silica gel, and elution with CH_2Cl_2 gave 2,2'-dithiobis[methyl 3-(1-methyl-3-indolyl)propanoate] [V: R_1 = H; R_2 = Me; R_2 = $(CH_2)_2COOMe$] (40) (0.38 g, 54%); mp (CH_2Cl_2/MeOH) 139-141.5°C.

^1H NMR ($CDCl_3$): δ 7.49 (1H, d, J = 8.0 Hz, ArH), 7.27 (1H, ddd, J = 8.3, 6.1, 0.9 Hz, ArH), 7.25 (1H, d, J = 8.1 Hz, ArH), 7.09 (1H, ddd, J = 8.0, 6.1, 1.9 Hz, ArH), 3.59, 3.53 (2x3H, 2xs, NCH_3, OCH_3), 2.76, 2.21 (2x2H, 2xt, J = 7.8 Hz, 3-CH_2CH_2).

^{13}C NMR ($CDCl_3$): δ 173.17 (s, $COOCH_3$), 138.49, 127.00, 126.09 (3xs, Ar), 124.14 (d, Ar), 123.77 (s, Ar), 119.68, 119.65, 109.87 (3xd, Ar), 51.39 (q, OCH_3), 35.09 (t, CH_2CO), 29.86 (q, NCH_3), 20.50 (t, 3-CH_2).

Analysis calculated for $C_{26}H_{28}N_2O_4S_2$ requires:

C, 62.9; H, 5.7; N, 5.7; S, 12.9%.

Found: C, 62.6; H, 5.6; N, 5.5; S, 13.0%.

A solution of (11) (0.53 g) in EtOH (10 mL) and 2N aqueous NaOH (3 mL) was stirred at 20°C for 80 minutes. The mixture was then diluted with water (100 mL) and extracted with CH_2Cl_2 (100 mL). The aqueous portion was adjusted to pH 2 with dilute HCl and extracted with EtOAc (3 x 120 mL). The EtOAc extracts were washed with water (150 mL) and the solvent removed under reduced pressure to give a yellow oil (0.48 g). This was redissolved in MeOH (7 mL) and 2 M aqueous NaOH (1 mL) and treated with NaBH (150 mg) for 5 minutes at 20°C. The mixture was then quenched with water and worked up as before to give a pale brown oil (0.46 g). Crystallization from CH/light petroleum gave 3-(1-methyl-2-thioxo-3-indolinyl)propanoic acid [R_1 = H; R_2 = Me; R_3 = $(CH_2)_2COOH$] (8) (0.32 g, 60%); mp 126-128.5°C.

^1H NMR ($CDCl_3$): δ 7.35 (2H, m, ArH), 7.18 (1H, td, J = 7.5, 0.9 Hz, ArH), 7.00 (1H, d, J = 7.8 Hz, ArH), 3.93 (1H, t, J = 5.3 Hz, H-3), 3.63 (3H, s, NCH_3), 2.51 (2H, m, 3-CH_2), 2.38 (1H, ddd, J = 16.1, 9.3, 6.7 Hz, CHCO), 2.06 (1H, ddd, J = 16.0, 9.8, 6.1 Hz, CHCO).
^{13}C NMR ($CDCl_3$): δ 204.61 (s, $CSNCH_3$), 178.41 (COOH), 145.88, 132.24 (2xs, Ar), 128.50, 124.38, 123.96, 109.57 (4xd, Ar), 56.05 (d, C-3), 31.37 (q, NCH_3), 29.16, 28.16 (2xt, 3-CH_2CH_2).
Analysis calculated for $C_{12}H_{13}NO_2S \cdot 0.25H_20$ requires:
C, 60.1; H, 5.6; N, 5.8; S, 13.4%.
Found: C, 60.0; H, 5.6; N, 5.9; S, 13.4%.

Similar hydrolysis of **40** (0.37 g) in EtOH/2 M aqueous NaOH for 3 hours at 20°C gave, after workup, a yellow oil (0.30 g). Crystallization from AcOH gave 2,2′-dithiobis[3-(1-methyl-3-indolyl)propanoic acid] [V: R_1 = H; R_2 = $(CH_2)_2COOH$; R_3 = Me] (37) (73 mg, 20%); mp 158.5-160°C.
^1H NMR ($(CD_3)_2CO$): δ 7.59 (1H, d, J = 8.1 Hz, ArH), 7.39 (1H, d, J = 8.0 Hz, ArH), 7.27 (1H, ddd, J = 8.2, 7.1, 0.9 Hz, ArH), 7.07 (1H, ddd, J = 8.1, 7.1, 0.8 Hz, ArH), 3.60 (3H, s, NCH_3), 2.79, 2.31 (2x2H, 2xt, J = 7.9 Hz, 3-CH_2CH_2).
^{13}C NMR ($(CD_3)_2CO$): δ 173.75 (s, COOH), 139.61, 127.54, 127.06 (3xs, Ar), 125.08 (d, Ar), 125.02 (s, Ar), 120.55, 120.53, 110.03 (3xd, Ar), 35.56 (t, CH_2CO), 30.13 (q, NCH_3), 21.32 (t, 3-CH_2).
Analysis calculated for $C_{24}H_{24}N_2O_4S_2$ requires:
C, 61.5; H, 5.2; N, 6.0; S, 13.7%.
Found: C, 61.5; H, 5.2; N, 6.1; S, 13.6%.

Chromatography of the mother liquors on silica gel, then treatment with $NaBH_4$ as above and crystallization of the products from CH_2Cl_2/light

petroleum also gave 3-(1-methyl-2-thioxo-3-indolinyl)-propanoic acid (8) (0.12 g, 32%).

Compounds 16, 18, 66, and 68 of Table 1

N-Alkylation of methyl 4-(3-indolyl)butanoate [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (2.14 g), with 18-crown-6 (0.26 g), potassium t-butoxide/CH_3I as above gave methyl 4-(1-methyl-3-indolyl)butanoate [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] (0.92 g, 40%) as a brown oil, which was used directly.
^1H NMR ($CDCl_3$): δ 7.58 (1H, dt, J = 7.9, 0.9 Hz, ArH), 7.28 (1H, d, J = 8.2 Hz, ArH), 7.21 (1H, ddd, J = 8.1, 7.0. 1.1 Hz, ArH), 7.09 (1H, ddd, J = 8.0, 7.0, 1.0 Hz, ArH), 6.84 (1H, s, ArH), 3.74 (3H, s, NCH_3), 3.66 (3H, s, $COOCH_3$), 2.79, 2.38 (2x2H, 2xt, J = 7.4 Hz, $\underline{CH_2}CH_2\underline{CH_2}CO$), 2.03 (2H, quin, J = 7.4 Hz, $CH_2\underline{CH_2}CH_2CO$).
^{13}C NMR ($CDCl_3$): δ 174.21 (s, $\underline{C}OOCH_3$), 137.08, 127.84 (2xs, ArH), 126.34, 121.50, 118.98, 118.62 (4xd, ArH), 114.07 (s, ArH), 109.13 (d, ArH), 51.44 (q, $COO\underline{C}H_3$), 33.68 (t, $\underline{C}H_2CO$), 32.55 (q, NCH_3), 25.58, 24.41 (2xt, 3-CH_2CH_2).
HREIMS *m/z* Found: M+ 231.1259.

4-(3-Indolyl)butanoic acid (1.04 g, 52%) was recovered by dissolving the filtered precipitates from the above reaction in water and acidifying; mp 124-126°C (Jackson RW, Manske RH, J. Am. Chem. Soc. 1930;52:5029 record mp 124°C).

Reaction of the ester [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] with DMSO/HCl as above gave crude 4-(1-methyl-2-oxo-3-indolinyl)butanoic acid [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] (0.84 g, 91% yield) as a brown oil.
^1H NMR ($CDCl_3$): δ 7.28 (1H, td, J = 7.7, 0.9 Hz, ArH), 7.25 (1H, d, J = 7.7 Hz, ArH), 7.06 (1H, td, J = 7.5,

0.9 Hz, ArH), 6.83 (1H, d, J = 7.8 Hz, ArH), 3.47 (1H, t, J = 5.9 Hz, H-3), 3.21 (3H, s, NCH_3), 2.37 (2H, t, J = 7.4 Hz, CH_2CO), 2.00, 1.69 (2x2H, 2xm, 3-CH_2CH_2).

An ice-cooled solution of the above crude oxoacid [III: R_1 = R_3 = H, R_2 = $(CH_2)_3COOMe$, R_3 = Me] (0.84 g) in ether (10 mL) was treated, dropwise with stirring, with an ethereal solution of diazomethane (from N-nitrosomethylurea, 1.2 g). After 30 minutes at 20°C, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (elution with EtOAc/light petroleum (1:2)) to give methyl 4-(1-methyl-2-oxo-3-indolinyl)butanoate [III: R_1 = R_3 = H, R_2 = $(CH_2)_3COOMe$, R_3 = Me] (0.64 g, 72%); mp (EtOAc/light petroleum) 69-71°C.

^{1}H NMR ($CDCl_3$): δ 7.28 (1H, t, J = 7.8 Hz, ArH), 7.26 (1H, d, J = 7.6 Hz, ArH), 7.05 (1H, td, J = 7.6, 0.7 Hz, ArH), 6.82 (1H, d, J = 7.7 Hz, ArH), 3.64 (3H, s, $COOCH_3$), 3.44 (1H, t, J = 6.0 Hz, H-3), 3.20 (3H, s, NCH_3), 2.33 (2H, t, J = 7.5 Hz, CH_2CO), 1.98, 1.68 (2x2H, 2xm, 3-CH_2CH_2).

^{13}C NMR ($CDCl_3$): δ 177.52 (s, $\underline{C}ONCH_3$), 173.59 (s, $\underline{C}OOCH_3$), 144.38, 128.71 (2xs, ArH), 128.00, 123.84, 122.40, 108.02 (4xd, ArH), 51.54 (q, $COO\underline{C}H_3$), 45.26 (d, C-3), 33.89, 29.98 (2xt, $\underline{C}H_2CH_2\underline{C}H_2CO$), 26.15 (q, NCH_3), 21.30 (t, 3-$CH_2\underline{C}H_2$).

Analysis calculated for $C_{14}H_{17}NO_3$ requires:
C, 68.0; H, 6.9; N, 5.7%.
Found: C, 67.9; H, 6.7; N, 5.7%.

The above oxoester [III: R_1 = R_3 = H, R_2 = $(CH_2)_3COOMe$, R_3 = Me] (0.90 g) was treated with P_2S_5 as above, followed by workup and chromatography on silica gel. Elution with CH_2Cl_2/light petroleum (3:2) gave methyl 4-(1-methyl-2-thioxo-3-indolyl)butanoate

[IV: R_1 = H, R_2 = $(CH_2)_3COOMe$, R_3 = Me] (18) (1.07 g, 79%); mp (benzene-light petroleum) 103-106°C.

^{1}H NMR ($CDCl_3$): δ 7.34 (2H, m, ArH), 7.19 (1H, td, J = 8.0, 0.9 Hz, ArH), 7.00 (dd, J = 8.0. 2.3).

Analysis calculated for $C_{14}H_{17}NO2S$ requires:

C, 63.9; H, 6.5; N, 5.3; S, 12.2%.

Found: C, 64.0; H, 6.4; N, 5.3; S, 12.3%.

A solution of 18 (0.47 g) in EtOAc (7 mL) was stirred with $FeCl_3$ (0.43 g) for 1 hour at 20°C, then worked up and chromatographed on silica gel. Elution with CH_2Cl_2 gave bis[methyl 1-methylindolyl-3-butanoate-(2)]disulfide [V: R_1 = H, R_2 = $(CH_2)_3COOMe$, R_3 = Me] (68) (0.40 g, 85%); mp (CH_2Cl_2/MeOH) 112-113°C.

^{1}H NMR ($CDCl_3$): δ 7.52 (1H, d, J = 8.0 Hz, ArH), 7.28 (1H, ddd, J = 8.2, 6.0. 1.0 Hz, ArH), 7.25 (1H, d, J = 8.0 Hz, ArH), 7.09 (1H, ddd, J = 8.0, 6.0. 1.9 Hz, ArH), 3.59, 3.55 (2x3H, 2xs, NCH_3, $COOCH_3$), 2.42, 2.07 (2x2H, 2xt, J = 7.4 Hz, $\underline{CH_2}CH_2\underline{CH_2}CO$), 1.68 (2H, quin, J = 7.4 Hz, $CH_2\underline{CH_2}CH_2CO$).

^{13}C NMR ($CDCl_3$): δ 173.82 (s, $\underline{C}OOCH_3$), 138.47, 127.23, 126.43, 124.74 (4xs, ArH), 124.05, 119.90, 119.49, 109.72 (4xd, ArH), 51.35 (q, $COO\underline{C}H_3$), 33.40 (t, $\underline{C}H_3CO$), 29.82 (q, NCH_3), 25.83, 24.17 (2xt, 3-CH_2CH_2).

Analysis calculated for $C_{28}H_{32}N_2O_4S_2$ requires:

C, 64.1; H, 6.1; N, 5.3; S, 12.2%.

Found: C, 63.9; H, 6.4; N, 5.3; S, 12.1%.

Hydrolysis of 18 with EtOH/H_2O/NaOH, followed by treatment with $NaBH_4$ and crystallization from CH_2Cl_2/light petroleum, as above, gave 4-(1-methyl-2-thioxo-3-indolyl)butanoic acid [IV: R_1 = H, R_2 = $(CH_2)_3COOH$, R_3 = Me] (16) (0.18 g, 44%); mp 144-146.5°C.

^1H NMR ($CDCl_3$): δ 7.34 (2H, m, ArH), 7.18 (1H, t, J = 7.6 Hz, ArH), 7.00 (1H, d, J = 7.7 Hz, ArH), 3.85 (1H, t, J = 5.5 Hz, H-3), 3.63 (3H, s, NCH_3), 2.34, 2.07 (2H, t, J = 7.6 Hz, CH_2CO), 2.28 2.18, 1.59, 1.40 (4x1H, 4xm, 3-CH_2CH_2).

^{13}C NMR ($CDCl_3$): δ 205.31 (s, $CSNCH_3$), 178.62 (s, COOH), 145.81, 133.06 (2xs, Ar), 128.20, 124.30, 123.86, 109.54 (4xd, Ar), 57.14 (d, C-3), 33.77, 33.01 (2xt, 3-$CH_2CH_2CH_2$), 31.42 (q, NCH_3), 20.11 (t, 3-CH_2CH_2).

Analysis calculated for $C_{13}H_{15}NO_2OS \cdot H_2O$ requires:

C, 61.6; H, 6.7; N, 5.5; S, 12.7%.

Found: C, 61.9; H, 6.3; N, 5.6; S, 12.8%.

Similar hydrolysis of 68 (0.40 g) gave, after workup, a yellow oil (0.37 g). Chromatography on silica gel, eluting with EtOAc/light petroleum (1:2) containing 1% AcOH, gave an oil (0.25 g). Crystallization from AcOH then gave 2,2'-dithiobis[4-(1-methyl-3-indolyl)butanoic acid] [V: R_1 = H, R_2 = $(CH_2)_3COOH$, R_3 = Me] (66) (0.17 g, 42%); mp 106.5-109.5°C.

^1H NMR ($CDCl_3$): δ 7.51 (1H, d, J = 8.0 Hz, ArH), 7.27 (2H, m, ArH), 7.08 (1H, ddd, J = 8.0, 6.0, 2.0 Hz, ArH), 3.55 (3H, s, NCH_3), 2.44 2.12 (2x2H, 2xt, J = 7.4 Hz, 3-$CH_2CH_2CH_2CO$), 1.68 (2H, quintet, J = 7.4 Hz, 3-$CH_2CH_2CH_2$).

^{13}C NMR ($CDCl_3$): δ 179.32 (s, COOH), 138.49, 127.49, 126.43, 124.56 (4xs, Ar), 124.14, 119,86, 119.62, 109.79 (4xd, Ar), 33.37 9t, CH_2CO), 29.86 (q, NCH_3) 25.59, 24.13 (2xt, 3-CH_2CH_2).

Analysis calculated for $C_{26}H_{28}N_2O_4S_2 \cdot 2CH_3COOH$ requires:

C, 58.4; H, 5.9; N, 4.5; S, 10.4%.

Found: C, 58.4; H, 5.9; N, 4.5; S, 10.6%.

EXAMPLE B

Preparation of Compounds 1, 29, 30, and 31 of Table 1 by the Method Outlined in Scheme 2

A solution of purified S_2Cl_2 (0.50 mL) in THF (20 mL) was added dropwise to a stirred, ice-cooled solution of 3-indolylacetic acid [II: $R_1 = R_3 = H$, $R_2 = CH_2COOH$] (2.20 g) in dry THF (30 mL) (method of Wieland T, Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146). After 30 minutes at 20°C the solvent was removed, and the residue was crystallized from aqueous acetic acid to give a yellow solid (1.00 g). Recrystallization of this solid from aqueous MeOH, followed by further crystallization from EtOAc-benzene gave bis[indolyl-3-acetic acid-(2)]trisulfide [VI: $R_1 = R_3 = H$, $R_2 = CH_2COOH$, n = 3] (30) as a yellow powder (80 mg, 3%); mp 199-202°C.

^{1}H NMR (CD_3COCD_3): δ 10.18 (1H, s, NH), 7.59 (1H, m, ArH), 7.06 (2H, m, ArH), 6.82 (1H, m, ArH), 3.99 (2H, s, CH_2CO).

^{13}C NMR (CD_3COCD_3): δ 173.30 (s, COOH), 138.82, 128.26, 127.03 (3xs, ArH), 124.76, 120.60, 120.33 (3xd, ArH), 116.97 (s, ArH), 112.16 (d, ArH), 30.89 (t, $\underline{C}H_2CO$).

Analysis calculated for $C_{20}H_{16}N_2O_4S_3$ requires:
C, 54.1; H, 3.6; N, 6.3; S, 21.6%.
Found: C, 54.1; H, 3.8; N, 6.0; S, 21.2%.

The mother liquors from the above aqueous methanol crystallization were evaporated, and the resulting solid was recrystallized from CH_2Cl_2 to give bis[indolyl-3-acetic acid-(2)]disulfide [[VI: $R_1 = R_3 = H$, $R_2 = CH_2COOH$, n = 2] (29) as a yellow solid (0.19 g, 7%); mp 196-199°C (Wieland T, Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146 record mp 208°C).

^1H NMR (CD_3COCD_3): δ 10.62 (1H, s, NH), 7.58 (1H, dd, J = 8.1, 0.6 Hz, ArH), 7.42 (1H, dt, J = 8.2. 0.8 Hz, ArH), 7.23 (1H, ddd, J = 8.2, 7.1, 0.9 Hz, ArH), 7.09 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 3.55 (2H, s, CH_2CO).

^{13}C NMR (CD_3COCD_3): δ 172.67 (s, COOH), 138.78, 128.33, 127.86 (3xs, ArH), 124.79, 120.72, 120.56 (3xd, ArH), 117.78 (s, ArH), 112.41 (d, ArH), 30.67 (t, $\underline{C}H_2CO$).

Analysis calculated for $C_{20}H_{16}N_2O_4S_2$ requires:

C, 58.2; H, 3.9; N, 6.8; S, 15.5%.

Found: C, 57.6; H, 4.4; N, 6.6; S, 15.3%.

Methylation of crude 30 with diazomethane as described above, followed by chromatography on silica gel, gave bis[methylindolyl-3-acetate-(2)]trisulfide [VI: $R_1 = R_3 = H$, $R_2 = CH_2COOMe$, n = 3] (31) (0.16 g, 47%); mp (CH_2Cl_2-light petroleum) 130-132°C.

^1H NMR ($CDCl_3$): δ 8.76 (1H, s, NH), 7.40 (1H, d, J = 8.0 Hz, ArH), 6.99 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 6.88 (1H, ddd, J = 8.2, 7.1, 0.9 Hz, ArH), 6.41 (1H, d, J = 8.2 Hz, ArH), 3.93 (2H, s, CH_2CO), 3.78 (3H, s, $COOCH_3$).

^{13}C NMR ($CDCl_3$): δ 172.93 (s, $\underline{C}OOCH_3$), 137.66, 127.02, 125.80 (3xs, ArH), 124.29, 120.06, 118.46 (3xd, ArH), 114.61 (s, ArH), 111.15 (d, ArH), 52.40 (q, $COO\underline{C}H_3$), 30.30 (t, $\underline{C}H_2CO$).

Analysis calculated for $C_{22}H_{20}N_2O_4S_3$ requires:

C, 55.9; H, 4.2; N, 5.9; S, 20.3%.

Found: C, 55.6; H, 4.4; N, 5.8; S, 19.9%.

Reduction of 29 with $NaBH_4/K_2CO_3$/MeOH as above gave 2-(2-thioxo-3-indolinyl)acetic acid [IV: $R_1 = R_3 = H$; $R_2 = CH_2COOH$] (1) (58 mg, 34%); mp (EtOAc/light petroleum) 166-168°C (Wieland T,

Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146 record mp 170-171°C).
^{1}H NMR ($(CD_3)_2CO$): δ 11.51 (1H, s, NH), 7.39 (1H, d, J = 7.9 Hz, ArH), 7.29 (1H, td, J = 7.7, 0.8 Hz, ArH), 7.11 (2H, m, ArH), 4.02 (1H, dd, J = 3.9, 8.4 Hz, H-3), 3.36 (1H, dd, J = 17.2, 3.9 Hz, 3-CH), 2.83 (1H, dd, J = 17.2, 8.4 Hz, 3-CH).

Compounds 4 and 28 of Table 1

Methyl 2-(1-methyl-3-indolyl)acetate [II: R_1 = H; R_2 = CH_2COOMe; R_3 = Me] (Guida WC, Mathre DJ, J. Org. Chem. 1980;45:3172-3176) (1.18 g) was treated with S_2Cl_2 (0.25 mL) as above and the product then chromatographed on silica gel. Elution with CH_2Cl_2/light petroleum (2:1) and CH_2Cl_2 gave a yellow oil, from which crystallization with EtOAc/light petroleum gave 2,2'-monothiobis[methyl 2-(1-methyl-3-indolyl)acetate] [VI: R_1 = H, R_2 = CH_2COOMe; R_3 = Me; n = 1] (0.17 g, 13%); mp 155-156°C.
^{1}H NMR ($CDCl_3$): 7.54 (1H, d, J = 8.0 Hz, ArH), 7.22 (2H, m, ArH), 7.11 (1H, ddd, J = 8.0, 4.9, 3.0 Hz, ArH), 3.96 (2H, s, 3-CH_2), 3.61 (3H, s, OCH_3), 3.48 (3H, s, NCH_3).
^{13}C NMR ($CDCl_3$): 171.54 (s, $COOCH_3$), 137.80, 126.80, 126.24 (3xs, Ar), 123.03, 119.92, 118.96 (3xd, Ar), 112.95 (s, Ar), 109.37 (d, Ar), 51.85 (q, OCH_3), 31.04 (t, 3-CH_2), 30.38 (q, NCH_3).
Analysis calculated for $C_{24}H_{24}N_2O_4S$ requires:
C, 66.1; H, 5.5; N, 6.4; S, 7.3%.
Found: C, 65.9; H, 5.6; N, 6.4; S, 7.4%.

Further crystallization of mother liquor fractions from benzene/light petroleum gave 2,2'-dithiobis[methyl 2-(1-methyl-3-indolyl)acetate] [VI: R_1 = H,

R_2 = CH_2COOMe; R_3 = Me; n = 2] (**28**) (0.16 g, 13%); mp 130-132.5°C.

^1H NMR ($CDCl_3$): 7.51 (1H, dt, *J* = 8.0, 0.8 Hz, ArH), 7.29 (2H, m, ArH), 7.12 (1H, ddd, *J* = 8.0, 6.0, 2.0 Hz, ArH), 3.57 (3H, s, OCH_3), 3.48 (3H, s, NCH_3), 3.33 (2H, s, 3-CH_2).

^{13}C NMR ($CDCl_3$): 171.44 (s, $COOCH_3$), 138.42, 128.13, 126.38 (3xs, Ar), 124.37, 120.13, 120.08 (3xd, Ar), 117.48 (s, Ar), 109.94 (d, Ar), 51.79 (q, OCH_3), 30.57 (q, NCH_3), 29.96 (t, 3-CH_2).

Analysis calculated for $C_{24}H_{24}N_2O_4S_2$ requires:
C, 61.5; H, 5.1; N, 6.0; S, 13.7%.
Found: C, 61.4; H, 5.2; N, 6.0; S, 13.8%.

The remaining mother liquor was treated successively with $NaBH_4$ and $FeCl_3$ as above, to give an additional 0.36 g (26%) of **28**.

Reduction of **28** with $NaBH_4$ as above gave methyl 2-(1-methyl-2-thioxo-3-indolinyl)acetate [IV: R_1 = H; R_2 = CH_2COOMe; R_3 = Me] (**4**) (61%); mp (benzene/light petroleum) 68-70°C.

^1H NMR ($CDCl_3$): 7.34 (2H, m, ArH), 7.16 (1H, td, *J* = 7.5, 0.9 Hz, ArH), 7.01 (1H, d, *J* = 7.8 Hz, ArH), 4.15 (1H, dd, *J* = 8.7, 4.1 Hz, H-3), 3.71 (3H, s, OCH_3), 3.65 (3H, s, NCH_3), 3.40 (1H, dd, *J* = 17.0, 4.1 Hz, 3-CH), 2.83 (1H, dd, *J* = 17.0, 8.7 Hz, 3-CH).

^{13}C NMR ($CDCl_3$): 204.24 (s, $CSNCH_3$), 171.68 (s, $COOCH_3$), 145.74, 132.95 (2xs, Ar), 128.47, 124.40, 123.96, 109.54 (4xd, Ar), 53.41 (d, C-3), 51.96 (q, OCH_3), 38.46 (t, 3-CH_2), 31.57 (q, NCH_3).

Analysis calculated for $C_{12}H_{13}NO_2S$ requires:
C, 61.3; H, 5.6; N, 6.0; S, 13.6%.
Found: C, 61.5; H, 5.8; N, 6.2; S, 13.9%.

Compounds 2 and 32 of Table 1

Similar treatment of 1-methyl-3-indolylacetic acid [II: R_1 = H, R_2 = CH_2COOH, R_3 = Me] (Guida WC, Mathre DJ, J. Org. Chem. 1980;45:3172; Kaestle KL, Anwer MK, Audhya TK, Goldstein G, Tetrahedron Lett. 1991;32:327) with S_2Cl_2 followed by chromatography on silica gel gave bis[1-methylindolyl-3-acetic acid-(2)]-disulfide [VI: R_1 = R_3 = H, R_2 = CH_2COOH, n = 2] (**32**) (0.10 g, 8%); mp (Me_2CO/light petroleum) 190-192.5°C (Wieland T, Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146 record mp 190-191°C).

^{1}H NMR (CD_3COCD_3): δ 7.56 (1H, dt, J = 8.1, 0.9 Hz, ArH), 7.44 (1H, d, J = 8.3 Hz, ArH), 7.31 (1H, ddd, J = 8.2, 7.0, 1.2 Hz, ArH), 7.11 (1H, ddd, J = 8.0, 7.0, 0.9 Hz, ArH), 3.65 (3H, s, NCH_3), 3.23 (2H, s, CH_2CO).

^{13}C NMR (CD_3COCD_3): δ 172.21 (s, COOH), 139.52, 128.56, 127.45 (3xs, ArH), 125.21, 120.91, 120.74 (3xd, ArH), 119.38 (s, ArH), 111.04 (d, ArH), 30.81 (t, $\underline{C}H_2CO$), 30.31 (q, NCH_3).

Analysis calculated for $C_{22}H_{20}N_2O_2S_2$ requires:

C, 60.0; H, 4.6; N, 6.4; S, 14.5%.

Found: C, 59.4; H, 4.9; N, 6.4; S, 15.0%.

Reduction of **32** with $NaBH_4/K_2CO_3$/MeOH as above gave 2-(1-methyl-2-thioxo-3-indolinyl)acetic acid [IV: R_1 = H; R_2 = CH_2COOH; R_3 = Me] (**2**) (62 mg, 60%); mp (CH_2Cl_2/light petroleum) 150-153°C (Wieland T, Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146 record mp 149-150°C).

^{1}H NMR ($CDCl_3$): δ 7.37 (2H, m, ArH), 7.18 (1H, t, J = 7.5 Hz, ArH), 7.02 (1H, d, J = 7.8 Hz, ArH), 4.14 (1H, dd, J = 8.6, 3.9 Hz, H-3), 3.65 (3H, s, NCH_3), 3.48 (1H, dd, J = 17.5, 4.0 Hz, 3-CH), 2.86 (1H, dd, J = 17.5, 8.7 Hz, 3-CH).

^{13}C NMR ($CDCl_3$): δ 203.88 (s, $CSNCH_3$), 176.31 (s, COOH), 145.67, 132.64 (2xs, Ar), 128.57, 124.52, 124.00, 109.59 (4xd, Ar), 53.07 (d, C-3), 38.33 (t, 3-CH_2), 31.59 (q, NCH_3).

Compounds 6 and 34 of Table 1

N-Benzyl 3-indolylacetamide [II: $R_1 = R_3 = H$, $R_2 = CH_2CONHCH_2Ph$] (Katritzky AR, J. Chem. Soc. 1955:2581) (1.48 g) was treated with S_2Cl_2 as above, and the product mixture was treated with $NaBH_4$ (ca. 0.7 g) in EtOH (10 mL) for 30 minutes at 20°C, then diluted with water (100 mL), acidified with dilute HCl and extracted in CH_2Cl_2 (2 x 100 mL) and EtOAc (100 mL). A sample from evaporation of the combined extracts was crystallized from EtOAc-light petroleum to give N-benzyl (2-thioxo-3-indolinyl)acetamide [IV: $R_1 = R_3 = H$, $R_2 = CH_2CONHCH_2Ph$] (6) (0.12 g, 7%); mp 193-195°C.

^1H NMR (CD_3SOCD_3): δ 12.64 (1H, s, NH), 8.50 (1H, t, J = 5.9 Hz, N$\underline{H}CH_2$), 7.32 (2H, t, J = 7.3 Hz, ArH), 7.25 (3H, m, ArH), 7.11 (1H, d, J = 7.3 Hz, ArH), 7.00 (1H, t, J = 8.0 Hz, ArH), 6.53 (1H, m, ArH), 4.34, 4.28 (2x1H, 2xdd, J = 15.3, 5.9 Hz, NHC$\underline{H}_2$), 4.04 (1H, dd, J = 9.5, 4.2 Hz, H-3), 3.10 (1H, dd, J = 15.3, 4.2 Hz, CH_2CO), 2.47 (1H, dd, J = 15.3, 9.5 Hz, CH_2CO).

^{13}C NMR (CD_3SOCD_3): δ 206.62 (s, CSNH), 169.41 (s, CONH), 143.97, 139.24, 134.36 (3xs, ArH), 128.22 (2xd, ArH), 127.95 (d, ArH), 127.36 (2xd, ArH), 126.77, 123.91, 123.09, 110.10 (4xd, ArH), 53.94 (d, C-3), 42.27, t, $NHCH_2$), 39.19 (t, $\underline{C}H_2CO$).

Analysis calculated for $C_{17}H_{10}N_2OS$ requires:

C, 68.9; H, 5.4; N, 9.5; S, 10.8%.

Found: C, 68.8; H, 5.8; N, 9.5; S, 10.7%.

The remaining product mixture (1.60 g) was treated with $FeCl_3$ as above then chromatographed on silica gel to give a yellow oil (1.40 g). Crystallization from EtOAc/light petroleum then EtOAc gave 2,2′-dithiobis[N-benzyl 2-(3-indolyl)acetamide] [VI: $R_1 = R_3 = H$; $R_2 = CH_2CONHCH_2Ph$] (34) (0.36 g, 22%); mp 200.5-203.5°C.

^{1}H NMR $(CD_3)_2SO$): δ 11.57 (1H, s, CSNH), 8.45 (1H, t, J = 5.9 Hz, $NHCH_2$), 7.53 (1H, d, J = 8.0 Hz, ArH), 7.30 (1H, d, J = 8.2 Hz, ArH), 7.29-7.14 (6H, m, ArH), 7.01 (1H, t, J = 7.5 Hz, ArH), 4.19 (2H, d, J = 5.9 Hz, $NHCH_2$), 3.44 (2H, s, 3-CH_2).

^{13}C NMR $(CD_3)_2SO$): δ 170.08 (9s, CONH), 139.36, 137.42 (2xs, Ar), 128.12, 127.13 (4xd, Ar), 127.12, 126.82 (2xs, Ar), 126.63, 123.41, 119.67, 119.09 (4xd, Ar), 116.83 (s, Ar), 111.43 (d, Ar), 42.25 (t, $NHCH_2$), 31.73 (t, 3-CH_2).

Analysis calculated for $C_{34}H_{30}N_4O_2S_2$ requires:

C, 62.6; H, 6.1; N, 5.6; S, 12.9%.

Found: C, 62.7; H, 6.3; N, 5.7; S, 13.0%.

<u>Compounds 13 and 47 of Table 1</u>

Esterification of 3-(3-indolyl)propanoic acid [II: $R_1 = R_2 = H$, $R_3 = (CH_2)_2COOH$] (1.50 g) with diazomethane as above gave methyl 3-(3-indolyl)-propanoate [II: $R_1 = R_2 = H$, $R_3 = (CH_2)_2COOMe$] (1.62 g, 100%) as a light brown oil. This was stirred with benzylamine (5 mL) at 140°C for 4 hours (Katritzky AR, <u>J. Chem. Soc.</u> 1955:2581-2586) to give, after workup and chromatography on silica gel, N-benzyl 3-(3-indolyl)-propanamide [II: $R_1 = R_2 = H$; $R_3 = (CH_2)_2CONHCH_2Ph$] (1.81 g, 88%); mp (EtOAc/light petroleum) 125-126.5°C.

^{1}H NMR ($CDCl_3$): 8.05 (1H, s, NH), 7.59 (1H, d, J = 7.8 Hz, ArH), 7.34 (1H, d, J = 7.9 Hz, ArH), 7.24

(3H, m, ArH), 7.18 (1H, dd, J = 7.9, 7.2 Hz, ArH), 7.10 (1H, dd, J = 7.9, 7.2 Hz, ArH), 7.07 (2H, m, ArH), 6.93 (1H, d, J = 1.9 Hz, H-2), 5.64 (1H, t, J = 5.7 Hz, N*H*CH_2), 4.35 (2H, d, J = 5.7 Hz, 2 H, NHC*H*$_2$), 3.13, 2.59 (2x2H, 2xt, J = 7.3 Hz, 3-CH_2CH_2).

^{13}C NMR ($CDCl_3$): 172.54 (s, CONH), 138.20, 136.35 (2xs, Ar), 128.58, 127.66 (4xd, Ar), 127.35 (d, Ar), 127.08 (s, Ar), 122.04, 121.88, 119.35, 118.68 (4xd, Ar), 113.79 (s, Ar), 111.21 (d, Ar), 43.51 (t, $NHCH_2$), 37.42 (t, *C*H_2CO), 21.38 (t, 3-CH_2).

Analysis calculated for $C_{18}H_{18}N_2O$ requires:

C, 77.7; H, 6.6; N, 10.1%.

Found: C; 77.4; H, 6.5; N, 10.3%.

The above amide [II: $R_1 = R_2 = H$, $R_3 = (CH_2)_2CONHCH_2Ph$] (1.74 g) was treated with S_2Cl_2, and the product mixture was treated successively with $NaBH_4$ and $FeCl_3$ as above, then chromatographed on silica gel. Elution with EtOAc/light petroleum (2:1) gave 2,2'-monothiobis[N-benzyl 3-(3-indolyl)-propanamide] [VI: $R_1 = R_2 = H$; $R_3 = (CH_2)_2CONHCH_2Ph$; n = 1] (0.10 g, 6%); mp (CH_2Cl_2/light petroleum) 218-219°C.

^1H NMR $(CD_3)_2SO$): 11.01 (1H, s, CSNH), 8.38 (1H, t, J = 5.7 Hz, N*H*CH_2), 7.56 (1H, d, J = 7.9 Hz, ArH), 7.26-7.03 (7H, 2xm, ArH), 6.97 (1H, t, J = 7.5 Hz, ArH), 4.26 (2H, d, J = 5.5 Hz, NHC*H*$_2$), 3.22, 2.55 (2x2H, 2xt, J = 7.6 Hz, 3-CH_2CH_2).

Analysis calculated for $C_{36}H_{34}N_4O_2S \cdot H_2O$ requires:

C, 72.6; H, 5.9; N, 9.4; S, 5.4%.

Found: C, 72.7; H, 5.9; N, 9.6; S, 5.7%.

Further elution with EtOAc/light petroleum (1:1) gave a yellow oil (1.10 g) from which crystallization with benzene/CH_2Cl_2/light petroleum gave 2,2'-dithiobis[N-benzyl 3-(3-indolyl)propanamide]

[VI: $R_1 = R_2 = H$, $R_3 = (CH_2)_2CONHCH_2Ph$; n = 2] (**47**) (0.73 g, 38%); mp (CH_2Cl_2/light petroleum) 141-144°C.
^{1}H NMR ($CDCl_3$): 8.47 (1H, s, CSNH), 7.51 (1H, d, *J* = 7.9 Hz, ArH), 7.27-7.20 (4H, m, ArH), 7.13 (1H, ddd, *J* = 8.2, 7.1, 1.1 Hz, ArH), 7.00 (3H, m, ArH), 5.01 (1H, t, *J* = 5.7 Hz, N*H*CH_2), 4.16 (2H, d, t, *J* = 5.7 Hz, NHC*H*$_2$), 2.88, 1.87 (2x2H, 2xt, *J* = 7.7 Hz, 3-CH_2CH_2).
^{13}C NMR ($CDCl_3$): 171.93 (s, CONH), 138.30, 137.27 (2xs, Ar), 128.51, 127.78 (4xd, Ar), 127.30 (d, Ar), 127.07, 125.66 (2xs, Ar), 124.43 (d, Ar), 123.93 (s, Ar), 120.18, 119.94, 111.23 (3xd, Ar), 43.39 (t, $NHCH_2$), 37.09 (t, *C*H$_2$CO), 20.56 (t, 3-CH_2).
Analysis calculated for $C_{36}H_{34}N_4O_2S_2$ requires:
C, 69.9; H, 5.5; N, 9.1; S, 10.3%.
Found: C, 69.7; H, 5.6; N, 9.1; S, 10.5%.

Reduction of **47** with $NaBH_4$ as above gave a quantitative yield of N-benzyl 3-(2-thioxo-3-indolinyl)propanamide [IV: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph$] (**13**); mp (CH_2Cl_2) 149.5-151°C.
^{1}H NMR ($(CD_3)_2CO$): 11.46 (1H, s, CSNH), 7.45 (1H, t, *J* = 6.0 Hz, N*H*CH_2), 7.42 (1H, d, *J* = 7.9 Hz, ArH), 7.32-7.16 (6H, m, ArH), 7.13 (1H, td, *J* = 7.5, 0.9 Hz, ArH), 7.09 (1H, d, *J* = 7.8 Hz, ArH), 4.37, 4.33 (2x1H, 2xdd, *J* = 15.0, 6.0 Hz, NHC*H*$_2$), 3.87 (1H, t, *J* = 5.4 Hz, H-3), 2.56, 2.34, 2.04 (4H, 3xm, 3-CH_2CH_2).
^{13}C NMR ($(CD_3)_2CO$): 208.79 (s, CSNH), 172.23 (s, CONH), 145.20, 140.69, 134.88 (3xs, Ar), 129.14 (d, 2e, Ar), 128.93 (d, Ar), 128.33 (d, 2e, Ar), 127.62, 125.27, 124.22, 110.78 (4xd, Ar), 57.57 (d, C-3), 43.46 (t, $NHCH_2$), 31.87, 30.09 (2xt, 3-CH_2CH_2).
Analysis calculated for $C_{18}H_{18}N_2OS$ requires:
C, 67.7; H, 6.0; N, 8.8; S, 10.0%.
Found: C, 67.3; H, 5.9; N, 8.9; S, 10.5%.

Compound 69 of Table 1

3-(3-Indolyl)butanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (1.10 g) was esterified with excess ethereal diazomethane to give methyl 4-(3-indolyl)butanoate [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (1.17 g, 100%); mp 73-75°C (Jackson RW, Manske RH, J. Am. Chem. Soc. 1930;52:5029 record mp 73-74°C). This was stirred with benzylamine (5 mL) at 150°C for 4 hours to give, after chromatography on silica gel (eluting with 1:4 EtOAc:CH_2Cl_2), *N*-benzyl-4-(3-indolyl)butanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3CONHCH_2Ph$] (1.43 g, 90%); mp (CH_2Cl_2/light petroleum) 123-124°C.

^{1}H NMR ($CDCl_3$): δ 8.05 (1H, br s, NH), 7.58 (1H, d, J = 7.9 Hz, ArH), 7.37-7.23 (6H, m, ArH), 7.18 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.10 (1H, ddd, J = 8.0, 7.0, 0.9 Hz, ArH), 6.95 (1H, d, J = 1.7 Hz, H-2), 5.68 (1H, br t, J = 5.7 Hz, N$\underline{H}$CH$_2$), 4.42 (1H, d, J = 5.7 Hz, NHC$\underline{H}_2$), 2.82 (2H, t, J = 7.3 Hz, 3-CH$_2$), 2.27 (2H, t, J = 7.5 Hz, CH$_2$CO), 2.09 (2H, pentet, J = 7.3 Hz, 3-CHC$\underline{H}_2$).

^{13}C NMR ($CDCl_3$): δ 172.79 (s, CONH), 138.35, 136.33 (2xs, Ar), 128.69, 127.84 (2d, 2x2C, Ar), 127.49 (d, Ar), 127.46 (s, Ar), 121.91, 121.50, 119.83, 118.3 (4xd, Ar), 115.57 (s, Ar), 111.10 (d, Ar), 43.58 (t, NCH$_2$), 36.15 (t, $\underline{C}$H$_2$CO), 26.06, 24.48 (2xt, 3-CH$_2$CH$_2$).

Analysis calculated for $C_{19}H_{20}N_2O$ requires:
C, 78.1; H, 6.9; N, 9.6%.
Found: C, 77.8; H, 6.8; N, 9.7%.

The above amide (1.38 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated with $NaBH_4$ as described above. The resulting oil was oxidized with 35% H_2O_2 (0.50 mL) in MeOH (10 mL) at 20°C for 20 minutes. Dilution with

water, extraction in CH_2Cl_2, and evaporation gave an oil which was chromatographed on silica gel. Elution with EtOAc/light petroleum (3:5) gave 2,2'-thiobis[*N*-benzyl-4-(3-indolyl)butanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_3CONHCH_2Ph$] (0.14 g, 10%); mp (CH_2Cl_2/light petroleum) 105.5-108°C (dec).
^{1}H NMR ($CDCl_3$): δ 10.25 (1H, s, NH), 7.49 (1H, d, *J* = 8.0 Hz, ArH), 7.35-7.25 (6H, m, ArH), 7.11 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, ArH), 7.01 (1H, ddd, *J* = 7.9, 7.0, 0.9 Hz, ArH), 5.75 (1H, t, *J* = 5.6 Hz, N<u>H</u>CH$_2$), 4.38 (2H, d, *J* = 5.7 Hz, NHC<u>H</u>$_2$), 3.07 (2H, t, *J* = 7.8 Hz, 3-CH$_2$), 2.38 (2H, t, *J* = 6.3 Hz, CH_2CO), 2.13 (2H, m, 3-CH$_2$<u>CH</u>$_2$).
^{13}C NMR ($CDCl_3$): δ 173.49 (s, CONH), 138.12, 136.97 (2xs, Ar), 128.73, 127.93 (2xd, 2x2C, Ar), 127.56 (d, Ar), 127.48, 124.00 (2xs, Ar), 122.53 (d, Ar), 119.79 (s, Ar), 119.07, 118.60, 111.52 (3xd, Ar), 43.79 (t, NCH_2), 35.66 (t, CH_2CO), 25.77, 24.38 (2xt, 3-CH_2CH_2).
Analysis calculated for $C_{38}H_{38}N_4O_2S$ requires:
C, 74.3; H, 6.2; N, 9.1; S, 5.2%.
Found: C, 74.2; H, 6.1; N, 9.1; S, 5.0%.

Elution with EtOAc:light petroleum (1:1) gave 2,2'-dithiobis[*N*-benzyl-4-(3-indolyl)butanamide] (69) [VI: n = 2; R_1 = R_3 = H, R_2 = $(CH_2)_3CONHCH_2Ph$] (0.55 g, 36%); mp (CH_2Cl_2/benzene) 98.5-101°C (dec).
^{1}H NMR ($(CD_3)_2CO$): δ 10.48 (1H, s, NH), 7.58 (1H, d, *J* = 8.0 Hz, ArH), 7.38 (1H, d, *J* = 8.2 Hz, ArH), 7.37 (1H, m, N<u>H</u>CH$_2$), 7.30-7.15 (6H, m, ArH), 7.03 (1H, ddd, *J* = 7.9, 7.3, 0.7 Hz, ArH), 4.30 (2H, d, *J* = 6.0 Hz, NHC<u>H</u>$_2$), 2.67 (2H, t, *J* = 7.6 Hz, 3-CH$_2$), 2.09 (2H, t, *J* = 7.5 Hz, CH_2CO), 1.84 (2H, pentet, *J* = 7.5 Hz, 3-CH$_2$C<u>H</u>$_2$).
^{13}C NMR ($(CD_3)_2CO$): δ 172.93 (s, CONH), 140.80, 138.83 (2xs, Ar), 129.12 (d, 2C, Ar), 128.46 (s, Ar), 128.35

(d, 2C, Ar), 127.58 (d, Ar), 126.71, 124.54, (2xs, Ar), 124.46, 120.60, 120.13, 112.36 (4xd, Ar), 43.43 (t, NCH_2), 36.34 (t, $\underline{C}H_2CO$), 27.75, 24.95 (2xt, 3-CH_2CH_2).
Analysis calculated for $C_{38}H_{38}N_4O_2S_2$ requires:
C, 70.6; H, 5.9; N,8.7; S, 9.9%.
Found: C, 70.4; H, 6.0; N, 8.8; S, 9.8%.

<u>Compound 35 of Table 1</u>

3-Indolylacetonitrile [II: $R_1 = R_3 = H$, $R_2 = CH_2CN$] (1.00 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated with $NaBH_4$ as described above. Crystallization of the resulting oil from CH_2Cl_2 gave 2,2'-thiobis[3-indolylacetonitrile] [VI: n = 1; $R_1 = R_3 = H$, $R_2 = CH_2CN$] (0.11 g, 10%); mp 237-240°C (Piotrowska H, Serafin B, Wejroch-Matacz K, <u>Rocz. Chem.</u> 1975;49:635 record mp 242-244°C).
^{1}H NMR ($(CD_3)_2SO$): δ 11.61 (1H, s, NH), 7.65 (1H, d, J = 8.0 Hz, ArH), 7.37 (1H, d, J = 8.2 Hz, ArH), 7.20 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 7.10 (1H, ddd, J = 8.0, 7.1, 0.8 Hz, ArH), 4.26 (2H, s, 3-CH_2).
^{13}C NMR: δ 136.52, 125.99, 123.92 (3xs, Ar), 123.25, 119.78 (2xd, Ar), 118.67 (s, Ar), 118.48, 111.60 (2xd, Ar), 108.78 (s, 3-$CH_2\underline{C}N$), 12.98 (t, 3-CH_2).
Analysis calculated for $C_{20}H_{14}N_4S \cdot 0.5H_2O$ requires:
C, 68.4; H, 4.3; N, 16.0; S, 9.2%.
Found: C, 68.4; H,4.2; N, 16.2; S, 9.1%.

The mother liquor was oxidized with H_2O_2 in MeOH as above, then the resulting solid was chromatographed on silica gel, eluting with CH_2Cl_2, to give 2,2'-dithiobis[3-indolylacetonitrile] (35) [VI: n = 2; $R_1 = R_3 = H$, $R_2 = CH_2CN$] (0.62 g, 52%); mp (CH_2Cl_2/MeOH) 168.5-169.5°C (Piotrowska H, Serafin B,

Wejroch-Matacz K, Rocz. Chem. 1975;49:635 record mp 169-170°C).

^{1}H NMR ($(CD_3)_2SO$): δ 11.90 (1H, s, NH), 7.67 (1H, d, J = 8.1 Hz, ArH), 7.42 (1H, d, J = 8.2 Hz, ArH), 7.28 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.14, (1H, ddd, J = 8.0, 7.1, 0.8 Hz, ArH), 3.69 (2H, s, 3-CH_2).

^{13}C NMR: δ 137.28, 126.36, 125.82 (3xs, Ar), 124.26, 120.03, 119.11, (3xd, Ar), 118.10 (s, Ar), 112.03 (d, Ar), 111.66 (s, 3-CH_2CN), 12.56 (t, 3-CH_2).

Analysis calculated for $C_{20}H_{14}N_4S_2$ requires:
C, 64.2; H, 3.7; N, 15.0; S, 17.1%.
Found: C, 64.1; H, 3.9; N, 15.1; S, 17.0%.

Compound 48 of Table 1

3-Indolylpropionitrile [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CN$] (Reppe W, Ufer H, German patent 698,273) (1.00 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$, then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with CH_2Cl_2, to give 2,2'-thiobis[3-indolylpropionitrile] [VI: n = 1; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CN$] (43 mg, 4%); mp (CH_2Cl_2/light petroleum) 204.5-207°C (Piotrowska H, Serafin B, Wejroch-Matacz K, Rocz. Chem. 1975;49:635 record mp 198-200°C).

^{1}H NMR ($(CD_3)_2SO$): δ 11.25 (1H, s, NH), 7.61 (1H, d, J = 7.9 Hz, ArH), 7.31 (1H, d, J = 7.8 Hz, ArH), 7.13 (1H, dd, J = 8.0, 7.1 Hz, ArH), 7.02 (1H, dd, J = 7.9, 7.1 Hz, ArH), 3.23, 2.71 (2x2H, 2xt, J = 7.2 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 136.65, 126.58, 124.04 (3xs, Ar), 122.65 (d, Ar), 120.36 (s, CN), 119.25, 118.79 (2xd, Ar), 116.32 (s, Ar), 111.31 (d, Ar), 20.60, 17.98 (2xt, 3-CH_2CH_2).

Further elution with CH_2Cl_2 gave 2,2'-dithiobis[3-indolylpropionitrile] (48) [VI: n = 2; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CN$] (0.82 g, 69%); mp (CH_2Cl_2) 167-169°C (Piotrowska H, Serafin B, Wejroch-Matacz K, Rocz. Chem. 1975;49:635 record mp 165-167°C).

^1H NMR ($(CD_3)_2SO$): δ 11.71 (1H, s, NH), 7.59 (1H, d, J = 8.0 Hz, ArH), 7.38 (1H, dt, J = 8.2, 0.8 Hz, ArH), 7.22 (1H, ddd, J = 8.2, 7.1, 1.1 Hz, ArH), 7.04 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 2.57, 2.37 (2x2H, 2xt, J = 7.2 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 137.48, 126.16, 125.59 (3xs, Ar), 123.88 (d, Ar), 120.39, 119.87 (2xs, Ar,CN), 119.45, 111.64 (2xd, Ar), 19.80, 17.97 (2xt, 3-CH_2CH_2).

Compound 49 of Table 1

A solution of gramine (8.4 g) and methyl nitroacetate (11.5 g) in xylene (50 mL) was stirred under nitrogen at 90-100°C for 5 hours (method of Lyttle DA, Weisblat DI, J. Am. Chem. Soc. 1947;69:2118). Evaporation gave an oil which was chromatographed on silica gel, eluting with CH_2Cl_2:light petroleum (1:1), to give 3-(2-nitroethyl)indole [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2NO_2$] (4.44 g, 48%); mp (benzene/light petroleum) 57-59.5°C (Somei M, Karasawa Y, Kaneko C, Heterocycles 1981;16:941 record mp (MeOH) 54-55°C).

^1H NMR ($CDCl_3$): δ 8.05 (1H, br s, NH), 7.57 (1H, d, J = 7.9 Hz, ArH), 7.37 (1H, dt, J = 8.2, 0.8 Hz, ArH), 7.22 (1H, ddd, J = 8.1, 7.0, 1.1 Hz, ArH), 7.16 (1H, ddd, J = 7.9, 7.1, 0.9 Hz, ArH), 7.04 (1H, d, J = 2.4 Hz, H-2), 4.66 (2H, t, J = 7.3 Hz, 3-$CH_2C\underline{H}_2$), 3.49 (2H, td, J = 7.3, 0.6 Hz, 3-CH_2).

^{13}C NMR: δ 136.25, 126.67 (2xs, Ar), 122.56, 122.54, 119.91, 118.13, 111.45 (5xd, Ar), 110.05 (s, Ar), 75.73 (t, 3-$CH_2\underline{C}H_2$), 23.63 (t, 3-CH_2).

The above nitroethyl compound (1.50 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with CH_2Cl_2:light petroleum (4:3), to give 2,2'-thiobis[3-(2-nitroethyl)indole] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_2NO_2$] (49 mg, 3%); mp (CH_2Cl_2/light petroleum) 134.5-136°C.

^1H NMR ($(CD_3)_2SO$): δ 11.26 (1H, s, NH), 7.59 (1H, d, J = 7.9 Hz, ArH), 7.30 (1H, d, J = 8.1 Hz, ArH), 7.13 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.02 (1H, ddd, J = 7.9, 7.1, 0.8 Hz, ArH), 4.71 (2H, t, J = 7.3 Hz, 3-$CH_2C\underline{H}_2$), 3.57 (2H, t, J = 7.3 Hz, 3-CH_2).

^{13}C NMR: δ 136.59, 126.60, 124.20 (3xs, Ar), 122.56, 119.27, 118.43 (3xd, Ar), 113.37 (s, Ar), 111.24 (d, Ar), 75.11 (t, 3-$CH_2\underline{C}H_2$, 22.69 (t, 3-CH_2).

Analysis calculated for $C_{20}H_{18}N_4O_4S$ requires:
C, 58.5; H, 4.4; N, 13.7; S, 7.8%.
Found: C, 58.3; H, 4.7; N, 13.6; S, 8.0%.

Further elution as above gave 2,2'-dithiobis[3-(2-nitroethyl)indole] (49) [VI: n = 2; R_1 = R_3 = H, R_2 = $(CH_2)_2NO_2$] (1.28 g, 73%); mp (CH_2Cl_2/light petroleum) 153-154°C.

^1H NMR ($(CD_3)_2SO$): δ 11.68 (1H, s, NH), 7.57 (1H, d, J = 8.0 Hz, ArH), 7.36 (1H, d, J = 8.2 Hz, ArH), 7.21 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.04 (1H, ddd, J = 7.9, 7.1, 0.8 Hz, ArH), 4.41 (2H, t, J = 7.2 Hz, 3-$CH_2C\underline{H}_2$), 2.97 (2H, t, J = 7.2 Hz, 3-CH_2).

^{13}C NMR: δ 137.37, 126.18, 125.95 (3xs, Ar), 123.76, 119.50, 119.08 (3xd, Ar), 117.39 (s, Ar), 111.59 (d, Ar), 75.05 (t, 3-$CH_2\underline{C}H_2$), 22.06 (t, 3-CH_2).
Analysis calculated for $C_{20}H_{18}N_4O_4S_2 \cdot 0.5H_2O$ requires:
C, 53.2; H, 4.2; N, 12.4; S, 14.2%.
Found: C, 53.4; H, 4.2; N, 12.6; S, 14.0%.

<u>Compounds 14 and 50 of Table 1</u>

DEPC (98%, 1.28 mL) was added to a stirred solution of 3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (1.30 g) and triethylamine (1.15 mL) in THF (15 mL) at 0°C. After 5 minutes the solution was saturated with ammonia gas, then the mixture was stirred at 20°C for 16 hours. The reaction was then quenched with water and extracted with EtOAc. Evaporation gave a solid, which was purified by chromatography on silica gel, eluting with EtOAc, to give 3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONH_2$] (1.09 g, 84%); mp (MeOH/water) 134-136°C (Crosby DG, Boyd JB, Johnson HE, <u>J. Org. Chem.</u> 1960;25:1826 record mp 131.5-133°C).
^{1}H NMR ($(CD_3)_2CO$): δ 9.95 (1H, s, NH), 7.58 (1H, dt, J = 8.2, 0.7 Hz, ArH), 7.36 (1H, dt, J = 8.1, 0.8 Hz, ArH), 7.13 (1H, m, H-2), 7.08 (1H, ddd, J = 8.1, 7.0, 1.1 Hz, ArH), 7.00 (1H, ddd, J = 8.0, 7.0, 1.0 Hz, ArH), 6.75, 6.12 (2xH, 2xbr s, $CONH_2$), 3.04 (2H, m, 3-CH_2), 2.05 (2H, m, 3-$CH_2C\underline{H}_2$).
^{13}C NMR: δ 174.87 (s, $CONH_2$), 137.75, 128.44 (2xs, Ar), 122.80, 122.02 (2xd, Ar), 119.30 (2xd, Ar), 115.67 (s, Ar), 112.08 (d, Ar), 37.05 (t, 3-$CH_2\underline{C}H_2$), 21.87 (t, 3-CH_2).

The above amide (1.03 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup

was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (3:1), to give firstly 2,2'-thiobis[3-(3-indolyl)-propanamide] [VI: $n = 1$; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONH_2$] (0.16 g, 14%); mp (EtOAc/light petroleum) 196.5-197.5°C.

^1H NMR ($(CD_3)_2SO$): δ 11.02 (1H, s, NH), 7.55 (1H, d, J = 8.0 Hz, ArH), 7.38 (1H, s, NH), 7.26 (1H, d, J = 8.1 Hz, ArH), 7.08 (1H, ddd, J = 8.0, 7.1, 0.8 Hz, ArH), 6.98 (1H, dd, J = 7.8, 7.1 Hz, ArH), 6.85 (1H, s, NH), 3.16, 2.46 (2x2H, 2xt, J = 7.7 Hz, 3-CH_2CH_2.

^{13}C NMR: δ 174.26 (s, $CONH_2$), 136.77, 126.82, 123.29 (3xs, Ar), 122.09, 118.82, 118.68 (3xd, Ar), 118.43 (s, Ar), 111.12 (d, Ar), 35.94 (t, 3-$CH_2\underline{C}H_2$), 20.58 (t, 3-CH_2).

Analysis calculated for $C_{22}H_{22}N_4O_2S$ requires:
C, 65.0; H, 5.4; N, 13.8; S, 7.9%.
Found: C, 64.8; H, 5.7; N, 13.6; S, 7.7%.

Further elution with EtOAc and EtOAc:EtOH (9:1) gave 2,2'-dithiobis[3-(3-indolyl)propanamide] **(50)** [VI: $n = 2$; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONH_2$] (0.90 g, 75%) as a yellow oil. A subsample crystallized from MeOH/dilute HCl as a solid which decomposed above 101°C.

^1H NMR $(CD_3)_2SO$): δ 11.37 (1H, s, NH), 7.55 (1H, d, J = 8.0 Hz, ArH), 7.32 (1H, d, J = 8.2 Hz, ArH), 7.16 (1H, t, J = 7.6 Hz, ArH), 7.00 (1H, t, J = 7.5 Hz, ArH), 6.94, 6.64 (2x1H, 2xs, $CONH_2$), 2.72, 2.14 (2x2H, 2xm, 3-CH_2CH_2).

^{13}C NMR: δ 173.48 (s, $CONH_2$), 137.42, 126.58, 125.09 (3xs, Ar), 123.29 (d, Ar), 122.65 (s, Ar), 119.53, 118.91, 111.46 (3xd, Ar), 36.48 (t, 3-$CH_2\underline{C}H_2$), 20.26 (t, 3-CH_2).

Analysis calculated for $C_{22}H_{22}N_4O_2S_2 \cdot 0.5H_2O$ requires:
C, 59.1; H, 5.2; N, 12.5; S, 14.3%.
Found: C, 59.1; H, 5.4; N, 12.2; S, 14.0%.

Reduction of (50) with $NaBH_4$ as above gave a quantitative yield of 3-(2-thioxo-3-indolinyl)-propanamide (14) [IV: $R_1 = R_2 = H$, $R_3 = (CH_2)_2CONH_2$]; mp (EtOAc) 160-163°C.

^{1}H NMR ($(CD_3)_2SO$): δ 12.63 (1H, s, NH), 7.38 (1H, d, J = 7.3 Hz, ArH), 7.27 (1H, t, J = 7.6 Hz, ArH), 7.22 (1H, s, NH), 7.12 (1H, t, J = 7.5 Hz, ArH), 7.00 (1H, d, J = 7.7 Hz, ArH), 6.70 (1H, s, NH), 3.84 (1H, t, J = 5.4 Hz, H-3), 2.38 (1H, m, 3-CH_2CH_2), 2.16-1.96 (2H, m, 3-CH_2CH_2), 1.77 (1H, ddd, J = 14.6, 10.3, 4.2 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 206.83 (s, CSNH), 173.37 ($CONH_2$), 144.11, 133.81 (2xs, Ar), 127.95, 124.11, 123.21, 110.03 (4xd, Ar), 56.35 (d, C-3), 30.12, 28.32 (2xt, 3-CH_2CH_2).

Analysis calculated for $C_{11}H_{12}N_2OS$ requires:
C, 60.0; H, 5.5; N, 12.7; S, 14.6%.
Found: C, 60.0; H, 5.5; N, 12.8; S, 14.3%.

Compound 51 of Table 1

DEPC (98%, 1.08 mL) was added to a stirred solution of 3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (1.10 g), triethylamine (1.94 mL) and methylamine hydrochloride (0.47 g) in THF (20 mL) at 0°C, then the mixture was stirred at 20°C for 20 hours. The reaction was then quenched with water and extracted with EtOAc. Evaporation gave an oil which was purified by chromatography on silica gel. Elution with EtOAc gave firstly foreruns, then *N*-methyl-3-(3-indolyl)-propanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHMe$] (0.81 g, 69%); mp (CH_2Cl_2/light petroleum) 97.5-99°C

(Kononova VV, Vereshchagin AL, Polyachenka VM, Semenov AA, Khim.-Farm. Zh. 1978;12:30 record mp 97-99°C).

^{1}H NMR ($(CD_3)_2CO$): δ 9.97 (1H, s, NH), 7.56 (1H, dd, J = 8.0, 0.8 Hz, ArH), 7.36 (1H, dt, J = 8.1, 0.8 Hz, ArH), 7.11 (1H, m, H-2), 7.08 (1H, ddd, J = 8.1, 7.0, 1.1 Hz, ArH), 6.99 (1H, ddd, J = 7.8, 7.0, 1.0 Hz, ArH), 6.99 (1H, br s, N$\underline{H}$CH$_3$), 3.04 (2H, td, J = 7.7, 0.9 Hz, 3-CH$_2$), 2.68 (3H, d, J = 4.7 Hz, NHC$\underline{H}_3$), 2.51 (2H, t, J = 7.7 Hz, 3-CH$_2$C$\underline{H}_2$).

^{13}C NMR: δ 173.30 (s, CONH), 137.73, 128.42 (2xs, Ar), 122.80, 122.01, 119.31 (3xd, Ar), 115.62 (s, Ar), 112.08 (d, Ar), 37.67 (t, 3-CH$_2$C$\underline{H}_2$), 26.06 (q, NCH$_3$), 22.08 (t, 3-CH$_2$).

The above N-methylpropanamide (0.75 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc, to give firstly 2,2'-thiobis[N-methyl-3-(3-indolyl)-propanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_2$CONHMe] (0.13 g, 16%); mp (EtOAc/benzene/light petroleum) 120-123°C.

^{1}H NMR ($CDCl_3$): δ 10.50 (1H, s, NH), 7.54 (1H, d, J = 7.9 Hz, ArH), 7.31 (1H, d, J = 8.1 Hz, ArH), 7.14 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.04 (1H, ddd, J = 7.9, 7.0, 0.9 Hz, ArH), 5.31 (1H, br d, J = 4.9 Hz, N$\underline{H}$CH$_3$), 3.47 (2H, m, 3-CH$_2$), 2.80 (2H, m, 3-CH$_2$C$\underline{H}_2$), 2.60 (3H, d, J = 4.9 Hz, NHC$\underline{H}_3$).

^{13}C NMR: δ 174.25 (s, CONH), 137.17, 126.67, 125.39 (3xs, Ar), 122.51, 118.86, 118.58 (3xd, Ar), 117.62 (s, Ar), 111.43 (d, Ar), 36.01 (t, 3-CH$_2$C$\underline{H}_2$), 26.27 (q, NCH$_3$), 21.02 (t, 3-CH$_2$).

Analysis calculated for $C_{24}H_{26}N_4O_2S \cdot C_6H_6$ requires:
C, 70.3; H, 6.3; N, 10.9; S, 6.3%.
Found: C, 70.1; H, 6.2; N, 11.0; S, 6.0%.

Further elution with EtOAc gave 2,2'-dithiobis[*N*-methyl-3-(3-indolyl)propanamide] (51) [V: n = 2; R_1 = R_3 = H, R_2 = $(CH_2)_2CONHMe$] (0.29 g, 34%); mp (EtOAc/benzene/light petroleum) 162.5-164°C.
^{1}H NMR (CD_3CD): δ 7.50 (1H, dt, *J* = 8.1, 0.8 Hz, ArH), 7.33 (1H, dt, *J* = 8.2, 0.8 Hz, ArH), 7.18 (1H, ddd, *J* = 8.1, 7.0, 1.0 Hz, ArH), 7.02 (1H, ddd, *J* = 8.0, 7.1, 0.8 Hz, ArH), 2.71 (2H, m, 3-CH_2), 2.49 (3H, s, NCH_3), 2.02 (2H, m, 3-$CH_2\underline{C}\underline{H}_2$).
^{13}C NMR: δ 175.76 (s, CONH), 139.27, 128.33, 127.01 (3xs, Ar), 124.80, (d, Ar), 123.92 (s, Ar), 120.48, 120.44, 112.48 (3xd, Ar), 38.44 (t, 3-$CH_2\underline{C}H_2$), 26.32 (q, NCH_3), 21.95 (t, 3-CH_2).
Analysis calculated for $C_{24}H_{26}N_4O_2S_2$ requires:
C, 61.8; H, 5.6; N, 12.0; S, 13.7%.
Found: C, 61.7; H, 5.7; N, 12.2; S, 13.7%.

Compound 52 of Table 1

A solution of 3-(3-indolyl)propanoic acid [II: R_1 = R_3 = H, R_2 = $(CH_2)_2COOH$] (0.70 g), triethylamine (5 mL) and methoxyamine hydrochloride (0.90 g) in THF (20 mL) was stirred at 20°C for 3 hours, then cooled to 0°C. DEPC (98%, 0.70 mL) was added, then the mixture was stirred at 20°C for 18 hours. The reaction was then quenched with water and extracted with EtOAc. Evaporation gave an oil which was purified by chromatography on silica gel. Elution with EtOAc:light petroleum (1:1) gave foreruns, then elution with EtOAc:light petroleum (3:1) gave *N*-methoxy-3-(3-indolyl)propanamide [II: R_1 = R_3 = H, R_2 = $(CH_2)_2CONHOMe$] (0.50 g, 62%); mp (CH_2Cl_2/light

petroleum) 116-118°C (Kononova VV, Vereshchagin AL, Polyachenka VM, Semenov AA, Khim.-Farm. Zh. 1978;12:30 record mp 114-115°C).

^{1}H NMR ($(CD_3)_2SO$): δ 10.97, 10.77 (2x1H, 2xs, 2xNH), 7.51 (1H, d, J = 7.8 Hz, ArH), 7.32 (1H, d, J = 8.1 Hz, ArH), 7.09 (1H, s, H-2), 7.06 (1H, td, J = 8.0, 1.0 Hz, ArH), 6.97 (1H, td, J = 8.0, 0.9 Hz, ArH), 3.55 (3H, s, $NHOC\underline{H}_3$), 2.91, 2.30 (2x2H, 2xt, J =7.6 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 168.72 (s, CONH), 136.13, 126.87 (2xs, Ar), 122.14, 120.83, 118.21, 118.09 (4xd, Ar), 113.30 (s, Ar), 111.23 (d, Ar), 63.00 (q, OCH_3), 33.20 (t, 3-$CH_2\underline{C}H_2$), 20.53 (t, 3-CH_2).

The above N-methoxypropanamide (1.00 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (3:2), to give firstly 2,2'-thiobis[*N*-methoxy-3-(3-indolyl)propanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_2CONHOMe$] (0.12 g, 11%); mp (EtOAc/light petroleum) 157.5-158.5°C.

^{1}H NMR ($(CD_3)_2SO$): δ 11.02, 10.95 (2x1H, 2xs, 2xNH), 7.53 (1H, d, J = 7.9 Hz, ArH), 7.25 (1H, d, J = 8.1 Hz, ArH), 7.09 (1H, t, J = 7.5 Hz, ArH), 6.99 (1H, t, J = 7.4 Hz, ArH), 3.52 (3H, s, $NHOC\underline{H}_3$), 3.17, 2.31 (2x2H, 2xt, J = 7.5 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 168.73 (s, CONH), 136.75, 126.79, 123.29 (3xs, Ar), 122.23 (d, Ar), 118.78 (d, 2C, Ar), 118.00 (s, Ar), 111.08 (d, Ar), 63.04 (q, OCH_3), 33.43 (t, 3-$CH_2\underline{C}H_2$), 20.46 (t, 3-CH_2).

Analysis calculated for $C_{24}H_{26}N_4O_4S$ requires:
C, 61.8; H, 5.6; N, 12.0; S, 6.9%.
Found: C, 61.6; H, 5.8; N, 12.2; S, 6.9%.

Elution with EtOAc gave 2,2'-dithiobis[*N*-methoxy-3-(3-indolyl)propanamide] (52) [VI: n = 2; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHOMe$] (0.35 g, 31%); mp (EtOAc/light petroleum) 176-178°C.
^1H NMR ($(CD_3)_2SO$): δ 11.39, 10.73 (2x1H, 2xs, 2xNH), 7.51 (1H, d, *J* = 8.0 Hz, ArH), 7.32 (1H, d, *J* = 8.2 Hz, ArH), 7.16 (1H, t, *J* = 7.7 Hz, ArH), 7.00 (1H, t, *J* = 7.5 Hz, ArH), 3.41 (3H, s, $NHOC\underline{H}_3$), 2.65, 2.01 (2x2H, 2xt, *J* = 7.4 Hz, 3-CH_2CH_2).
^{13}C NMR: δ 168.21 (s, CONH), 137.42, 126.52, 125.16 (3xs, Ar), 123.37 (d, Ar), 122.20 (s, Ar), 119.48, 118.96, 111.48 (3xd, Ar), 62.91 (q, OCH_3), 33.79 (t, 3-$CH_2\underline{C}H_2$), 20.09 (t, 3-CH_2).
Analysis calculated for $C_{24}H_{26}N_4O_4S_2$ requires:
C, 57.8; H, 5.2; N, 11.2; S, 12.9%.
Found: C, 57.6; H, 5.4; N, 11.3; S, 12.7%.

<u>Compound 53 of Table 1</u>

DEPC (98%, 1.28 mL) was added to a stirred solution of 3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (1.04 g) and triethylamine (1.15 mL) in THF (15 mL) at 0°C. After 5 minutes the solution was saturated with dimethylamine gas, then the mixture was stirred at 20°C for 16 hours. Workup as above and chromatography on silica gel, eluting with EtOAc, gave *N*,*N*-dimethyl 3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONMe_2$] (0.90 g, 76%); mp (CH_2Cl_2/light petroleum) 141-142°C (Avramenko VG, Suvorov NN, Mashkovskii MD, Mushulov PI, Eryshev BYa, Fedorova VS, Orlova IA, Trubitsyna TK, <u>Khim.-Farm. Zh.</u> 1970;4:10 record mp 139-140.5°C).
^1H NMR (CD_3OD): δ 7.53 (1H, dt, *J* = 7.9, 0.9 Hz, ArH), 7.32 (1H, dt, *J* = 8.1, 0.8 Hz, ArH) 7.07 (1H, ddd,

J = 8.1, 7.0, 1.1 Hz, ArH), 7.04 (s, H-2), 6.99 (1H, ddd, J = 7.9, 7.0, 0.9 Hz, ArH), 3.05 (2H, m, 3-CH_2), 2.88, 2.86 (2x3H, 2xs, $N(CH_3)_2$, 2.73 (2H, m, 3-$CH_2\underline{C}\underline{H}_2$).
^{13}C NMR: δ 175.75 (s, $\underline{C}ON(CH_3)_2$), 138.20, 128.59 (2xs, Ar), 123.11, 122.36, 119.61, 119.24 (4xd, Ar), 115.16 (s, Ar), 112.26 (d, Ar), 37.89, 35.82 (2xq, $N(CH_3)_2$), 35.30 (t, 3-$CH_2\underline{C}H_2$), 22.32 (t, 3-CH_2).

The above dimethylpropanamide (0.82 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (3:2), to give firstly 2,2'-thiobis-[*N*,*N*-dimethyl-3-(3-indolyl)propanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_2CONHMe_2$] (0.12 g, 14%); mp (EtOAc/light petroleum) 189-190°C.
^1H NMR ($CDCl_3$): δ 10.72 (br s, 1 H, NH), 7.55 (1H, d, J = 7.9 Hz, ArH), 7.24 (1H, d, J = 8.1 Hz, ArH), 7.10 (ddd, J = 8.0, 7.1, 0.9 Hz, 1 H, ArH), 7.02 (dd, J = 7.9, 7.1 Hz, 1 H, ArH), 3.47, 2.97 (2x2H, 2xm, 3-CH_2CH_2), 2.95, 2.91 (2x3H, 2xs, $N(CH_3)_2$).
^{13}C NMR: δ 173.36 (s, $\underline{C}ON(CH_3)_2$), 137.15, 126.92, 125.55 (3xs, Ar), 122.26, 118.68, 118.58 (3xd, Ar), 118.02 (s, Ar), 111.35 (d, Ar), 37.49, 35.74 (2xq, $N(CH_3)_2$), 32.14 (t, 3-$CH_2\underline{C}H_2$), 20.54 (t,3-CH_2).
Analysis calculated for $C_{26}H_{30}N_4O_2S$ requires:
C, 67.5; H, 6.5; N, 12.1; S, 6.9%.
Found: C, 67.4; H, 6.6; N, 12.0; S, 7.2%.

Elution with EtOAc gave 2,2'-dithiobis-[*N*,*N*-dimethyl-3-(3-indolyl)propanamide] (**53**) [VI: n = 2; R_1 = R_3 = H, R_2 = $(CH_2)_2CONMe_2$] (0.49 g, 52%); mp (EtOAc) 179-180°C.
^1H NMR (CD_3OD): δ 7.45 (1H, dt, J = 8.0, 0.8 Hz, ArH), 7.32 (1H, dt, J = 8.2, 0.8 Hz, ArH), 7.17 (1H, ddd,

J = 8.2, 7.1, 1.1 Hz, ArH), 7.01 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 2.72 (2H, m, 3-C$\underline{H}_2$CH_2), 2.71, 2.44 (2x3H, 2xs, N(C$\underline{H}_3$)$_2$), 2.09 (2H, m, 3-CH_2C$\underline{H}_2$).
^{13}C NMR: δ 174.68 (s, $\underline{C}$ON(CH_3)$_2$), 139.43, 128.26, 126.61 (3xs, Ar), 124.85 (d, Ar), 123.84 (s, Ar), 120.55, 120.28, 112.51 (3xd, Ar), 37.57 (q, NCH_3), 35.69 (t, 3-CH_2CH_2), 35.60 (q, NCH_3), 21.49 (t, 3-CH_2).
Analysis calculated for $C_{26}H_{30}N_4O_2S_2$ requires:
C, 63.2; H, 6.1; N, 11.3; S, 13.0%.
Found: C, 63.2; H, 6.2; N, 11.3; S, 13.1%.

Compound 54 of Table 1

DEPC (98%, 0.69 mL) was added to a stirred solution of 3-(3-indolyl)-propanoic acid [II: R_1 = R_3 = H, R_2 = (CH_2)$_2$COOH] (0.70 g) and phenethylamine (1.1 mL) in THF (15 mL) at 0°C, then the mixture was stirred at 20°C for 3 hours. Workup and chromatography on silica gel, eluting with EtOAc/light petroleum (1:1) gave *N*-(2-phenylethyl)-3-(3-indolyl)-propanamide [II: R_1 = R_3 = H, R_2 = (CH_2)$_2$CONH(CH_2)$_2$Ph] (0.58 g, 54%); mp (EtOAc/light petroleum) 88-89°C.
^{1}H NMR (CDCl_3): δ 8.02 (1H, br s, NH), 7.58 (1H, d, J = 7.9 Hz, ArH), 7.36 (1H, d, J = 8.1 Hz, ArH), 7.24-7.15 (4H, m, ArH), 7.12 (1H, ddd, J = 7.9, 7.0, 0.8 Hz, ArH), 6.99 (2H, dd, J = 7.4, 1.7 Hz, ArH), 6.95 (1H, d, J = 2.2 Hz, H-2), 5.34 (1H, br t, J = 6.0 Hz, N$\underline{H}$CH_2), 3.44 (2H, q, J = 6.6 Hz, NHC$\underline{H}_2$), 3.09 (2H, t, J = 7.3 Hz, 3-CH_2), 2.66 (2H, t, J = 6.9 Hz, NHCH_2C$\underline{H}_2$), 2.52 (2H, t, J = 7.3 Hz, 3-CHC$\underline{H}_2$).
^{13}C NMR: δ 172.64 (s, CONH), 138.90, 136.38 (2xs, Ar), 128.71, 128.58 (2xd, 2x2C, Ar), 127.13 (s, Ar), 126.41, 122.10, 121.77, 119.37, 118.72 (5xd, Ar), 114.95 (s, Ar), 111.23 (d, Ar), 40.48, 37.42, 35.62 (3xt, 3-CH_2CH_2CONH($\underline{C}H_2$)$_2$), 21.35 (t, 3-CH_2).

Analysis calculated for $C_{19}H_{20}N_2O$ requires:

C, 78.1; H, 6.9; N, 9.6%.

Found: C, 77.9; H, 7.0; N, 9.6%.

The above phenylethylpropanamide (0.53 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (1:2), to give firstly 2,2'-thiobis[*N*-(2-phenylethyl)-3-(3-indolyl)-propanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_2CONH(CH_2)_2Ph$] (0.13 g, 23%); mp (EtOAc/light petroleum) 120-121.5°C.

^{1}H NMR ($CDCl_3$): δ 10.69 (1H, s, NH), 7.55 (1H, d, J = 7.9 Hz, ArH), 7.35 (1H, d, J = 8.2 Hz, ArH), 7.17 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.08 (1H, ddd, J = 8.0, 0.9 Hz, ArH), 7.02 (1H, t, J = 7.4 Hz, ArH), 6.93 (2H, t, J = 7.4 Hz, ArH), 6.33 (2H, d, J = 7.2 Hz, ArH), 5.26 (1H, t, J = 5.9 Hz, N$\underline{H}CH_2$), 3.51 (2H, m, 3-CH_2), 3.14 (2H, q, J = 6.6 Hz, NHC$\underline{H}_2$), 2.77 (2H, m, 3-$CH_2C\underline{H}_2$), 1.92 (2H, t, J = 6.8 Hz, $NHCH_2C\underline{H}_2$).

^{13}C NMR: δ 173.62 (s, CONH), 138.20, 137.33 (2xs, Ar), 128.40, 128.36 (2xd, 2x2C, Ar), 126.76 (s, Ar), 126.16 (d, Ar), 125.51 (s, Ar), 122.78, 119.17, 118.70 (3xd, Ar), 117.57 (s, Ar), 111.70 (d, Ar), 40.49, 36.43, 35.46 (3xt, 3-$CH_2\underline{C}H_2CONH(\underline{C}H_2)_2$), 21.35 (t, 3-$CH_2$).

Analysis calculated for $C_{38}H_{38}N_4O_2S$ requires:

C, 74.2; H, 6.2; N, 9.1; S, 5.2%.

Found: C, 74.4; H, 6.4; N, 9.0; S, 5.2.%

Elution with EtOAc:light petroleum (2:3) gave 2,2'-dithiobis[*N*-(2-phenylethyl)-3-(3-indolyl)-propanamide] (54) [VI: n = 2; R_1 = R_3 = H, R_2 = $(CH_2)_2CONH(CH_2)_2Ph$] (0.36 g, 61%) as an oil.

^{1}H NMR ($CDCl_3$): δ 8.42 (1H, s, NH), 7.51 (1H, d, J = 8.0 Hz, ArH), 7.32-7.16 (5H, m, ArH), 7.04 (3H, m, ArH), 4.63 (1H, t, J = 5.9 Hz, N$\underline{H}$$CH_2$), 3.23 (2H, q, J = 6.7 Hz, NHC$\underline{H}_2$, 2.85 (t, J = 7.8 Hz, 3-CH_2), 2.59 (2H, t, J = 7.0 Hz, $NHCH_2C\underline{H}_2$), 1.81 (2H, t, J = 7.8 Hz, 3-$CH_2C\underline{H}_2$).
^{13}C NMR: δ 171.95 (s, CONH), 139.15, 137.23 (2xs, Ar), 128.87, 128.55 (2xd, 2x2C, Ar), 127.02 (s, Ar), 126.39 (d, Ar), 125.50 (s, Ar), 124.33 (d, Ar), 123.98 (s, Ar), 120.11, 119.88, 111.17 (3xd, Ar), 40.62, 37.37, 35.58 (3xt, 3-$CH_2\underline{H}_2$CONH($\underline{C}H_2)_2$), 20.64 (t, 3-CH_2).
HRFABMS *m/z* calculated for $C_{38}H_{39}N_4O_2S_2$:
647.2514 (MH^+)
Found: 647.2471.

<u>Compounds 55 and 56 of Table 1</u>

A solution of 3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (0.80 g), triethylamine (10 mL) and methyl 4-(aminomethyl)benzoate hydrochloride (Nair MG, Baugh CM, <u>J. Org. Chem.</u> 1973;38:2185) (1.29 g) in THF (20 mL) was stirred at 20°C for 15 minutes, then cooled to 0°C. DEPC (98%, 1.00 mL) was added, then the mixture was stirred at 20°C for 18 hours. Workup and chromatography on silica gel, eluting with EtOAc:light petroleum (5:3) gave *N*-(4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph\{4\text{-}COOMe\}$] (1.10 g, 77%); mp ($CH_2Cl_2$/light petroleum) 130-132°C.
^{1}H NMR ($CDCl_3$): δ 8.08 (1H, s, NH), 7.88 (2H, d, J = 8.2 Hz, ArH), 7.60 (1H, d, J = 7.8 Hz, ArH), 7.36 (1H, d, J = 8.1 Hz, ArH), 7.19 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.11 (1H, ddd, J = 7.9, 7.2, 0.7 Hz, ArH), 7.06 (2H, d, J = 8.2 Hz, ArH), 6.94 (1H, d, J = 2.3 Hz, H-2), 5.74 (1H, br t, J = 5.9 Hz, N$\underline{H}$$CH_2$),

4.38 (2H, d, J = 5.9 Hz, NHC$\underline{H}_2$), 3.90 (3H, s, OCH_3), 3.15, 2.63 (2x2H, 2xt, J = 7.2 Hz, 3-CH_2CH_2).
^{13}C NMR: δ 172.68 (s, CONH), 166.87 (s, $\underline{C}OOCH_3$), 143.50, 136.37 (2xs, Ar), 129.80 (2xd, Ar), 129.10 (s, Ar), 127.28 (2xd, Ar), 127.03 (s, Ar), 122.11, 121.92, 119.41, 118.64 (4xd, Ar), 114.66 (s, Ar), 111.27 (d, Ar), 52.09 (q, OCH_3), 43.05 (t, $NHCH_2$), 37.37 (t, 3-$CH_2\underline{C}H_2$), 21.39 (t, 3-CH_2).
Analysis calculated for $C_{20}H_{20}N_2O_3$ requires:
C, 71.4; H, 6.0; N, 8.3%.
Found: C, 71.1; H, 5.7; N, 8.4%.

The above methoxycarbonylbenzylpropanamide (1.08 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (2:3), to give firstly 2,2'-thiobis[*N*-(4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_2CONHCH_2Ph\{4\text{-}COOMe\}$] (0.18 g, 16%); mp (MeOH/dilute HCl) 101-104.5°C (dec).
^{1}H NMR ($CDCl_3$): δ 10.28 (1H, s, NH), 7.47 (1H, d, J = 7.7 Hz, ArH), 7.45 (2H, d, J = 8.4 Hz, ArH), 7.05 (1H, d, J = 8.0 Hz, ArH), 6.97 (1H, ddd, J = 8.0, 6.9, 1.1 Hz, ArH), 6.91 (1H, ddd, J = 7.9, 6.8, 1.1 Hz, ArH), 6.61 (2H, d, J = 8.3 Hz, ArH), 6.34 (1H, br t, J = 5.8 Hz, N$\underline{H}$CH$_2$), 4.40 (2H, d, J = 5.9 Hz, NHC$\underline{H}_2$), 3.79 (3H, s, OCH_3) 3.54, 2.97 (2x2H, 2xm, 3-CH_2CH_2).
^{13}C NMR: δ 174.37 (s, CONH), 166.75 (s, $\underline{C}OOCH_3$), 142.31, 137.15 (2xs, Ar), 129.35 (d, 2C, Ar), 128.39, 126.52 (2xs, Ar), 126.24 (d, 2C, Ar), 125.30 (s, Ar), 122.65, 118.87, 118.49 (3xd, Ar), 117.92 (s, Ar), 111.31 (d, Ar), 51.95 (q, OCH_3), 43.22 (t, $NHCH_2$), 36.34 (t, 3-$CH_2\underline{C}H_2$), 21.17 (t, 3-CH_2).

Analysis calculated for $C_{40}H_{38}N_4O_6S \cdot 0.5H_2O$ requires:

C, 67.5; H, 5.5; N, 7.9%.

Found: C, 67.4; H, 5.4; N, 8.1%.

Elution with EtOAc:light petroleum (1:1) gave 2,2'-dithiobis[*N*-(4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide] (55) [VI: n = 2; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph\{4\text{-}COOMe\}$] (0.50 g, 42%); mp (EtOAc/light petroleum) 151-153°C.

^1H NMR (($(CD_3)_2SO$): δ 11.42 (1H, s, NH), 8.06 (1H, t, J = 5.7 Hz, N$\underline{H}CH_2$), 7.81 (2H, d, J = 8.2 Hz, ArH), 7.55 (1H, d, J = 8.0 Hz, ArH), 7.34 (1H, d, J = 8.2 Hz, ArH), 7.17 (1H, t, J = 7.6 Hz, ArH), 7.11 (2H, d, J = 8.1 Hz, ArH), 6.99 (1H, t, J = 7.5 Hz, ArH), 4.19 (2H, d, J = 5.8 Hz, $NHC\underline{H}_2$), 3.84 (3H, s, OCH_3), 2.73, 2.24 (2x2H, 2xt, J = 7.5 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 171.48 (s, CONH), 166.00 (s, $\underline{C}OOCH_3$), 145.01, 137.37 (2xs, Ar), 128.98 (d, 2C, Ar), 127.84 (s, Ar), 127.01 (d, 2C, Ar), 126.53, 125.21 (2xs, Ar), 123.24 (d, Ar), 122.39 (s, Ar), 119.57, 118.86, 111.38 (3xd, Ar), 51.93 (q, OCH_3), 41.62 (t, $NHCH_2$), 36.65 (t, 3-$CH_2\underline{C}H_2$), 20.38 (t, 3-CH_2).

Analysis calculated for $C_{40}H_{38}N_4O_6S_2$ requires:

C, 65.4; H, 5.2; N, 7.6; S, 8.7%.

Found: C, 65.5; H, 5.5; N, 7.3; S, 8.8%.

Hydrolysis of 55 (0.24 g) with K_2CO_3 in MeOH/water at 30°C for 1 day, then 50°C for 1 hour, under nitrogen as above gave an oil. Chromatography on silica gel, eluting with EtOAc:light petroleum (1:1) containing 1% AcOH, gave 2,2'-dithiobis[*N*-(4-carboxybenzyl)-3-(3-indolyl)propanamide] (56) [VI: n = 2; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph\{4\text{-}COOH\}$] (60 mg, 26%); mp (MeOH/dilute HCl) 135.5-138.5°C (decomposed).

^1H NMR $(CD_3)_2SO$): δ 11.41 (1H, s, NH), 8.03 (1H, t, J = 5.8 Hz, N$\underline{H}CH_2$), 7.79 (2H, d, J = 8.2 Hz, ArH), 7.55

(1H, d, J = 8.0 Hz, ArH), 7.33 (1H, d, J = 8.2 Hz, ArH), 7.16 (1H, t, J = 7.6 Hz, ArH), 7.09 (2H, d, J = 8.1 Hz, ArH), 6.99 (1H, t, J = 7.5 Hz, ArH), 4.18 (2H, d, J = 5.8 Hz, $NHC\underline{H}_2$), 2.73, 2.23 (2x2H, 2xt, J = 7.5 Hz, 3-CH_2CH_2).
^{13}C NMR: δ 171.44 (s, CONH), 167.10 (s, COOH), 144.46, 137.37 (2xs, Ar), 129.14 (d, 2C, Ar), 129.05 (s, Ar), 126.87 (d, 2C, Ar), 126.53, 125.18 (2xs, Ar), 123.23 (d, Ar), 122.40 (s, Ar), 119.58, 118.85, 111.37 (3xd, Ar), 41.65 (t, $NHCH_2$), 36.42 (t, 3-$CH\underline{C}H_2$), 20.37 (t, 3-CH_2).

Analysis calculated for $C_{38}H_{34}N_4O_6S_2 \cdot H_2O$ requires:
C, 63.0; H, 5.0; N, 7.7; S, 8.8%.
Found: C, 62.5; H, 5.2; N, 8.2; S, 8.8%.

<u>Compounds 57 and 58 of Table 1</u>

A stirred solution of methyl 2-acetoxy-4-bromomethylbenzoate (Regnier G, Canevari R, Le Douarec J-C, <u>Bull. Soc. Chim. Fr.</u> 1966:2821) (10.7 g) and hexamethylenetetramine (17.1 g) in $CHCl_3$ (150 mL) was refluxed for 5 hours, then the solvent was removed (method of Meindl W, v Angerer E, Ruckdeschel G, Schonenberger H, <u>Arch. Pharm. (Weinheim)</u> 1982;315:941). The residue was stirred with MeOH (60 mL) and concentrated HCl (30 mL) at 20°C for 10 minutes, then the solvent removed. Treatment of the solid residue twice more with HCl/MeOH and evaporation gave a solid, which was washed with CH_2Cl_2, then treated with saturated $KHCO_3$ solution. The base was extracted with EtOAc and CH_2Cl_2, then the solvents removed. The crude hydrochloride salt (5.30 g, 70% pure) was precipitated from an ethereal solution of the base upon the addition of HCl gas. A subsample of the

above crude base was purified by chromatography on silica gel, eluting with EtOAc/light petroleum (1:2). Acidification of a solution of the purified base gave pure methyl 4-(aminomethyl)-2-hydroxybenzoate hydrochloride; mp (CH_2Cl_2/light petroleum) 225-227°C.
^{1}H NMR $(CD_3)_2SO$): δ 10.56 (1H, s, OH), 8.58 (3H, br s, NH_3^+), 7.78 (1H, d, J = 8.1 Hz, H-6), 7.14 (1H, s, H-3), 7.05 (1H, d, J = 8.1 Hz, H-5), 4.01 (2H, br s, 4-CH_2), 3.88 (3H, s, OCH_3).
^{13}C NMR: δ 168.81 (s, $\underline{C}OOCH_3$), 159.80 (s, C-2), 141.84 (s, C-4), 130.25 (d, C-6), 119.61 (d, C-5), 117.48 (d, C-3), 112.90 (s, C-1), 52.53 (q, OCH_3), 41.63 (t, 4-CH_2).
Analysis calculated for $C_9H_{11}NO_3 \cdot HCl \cdot 0.5H_2O$ requires:
C, 47.7; H, 5.8; N, 6.2; Cl, 15.7%.
Found: C, 47.9; H, 5.8; N, 6.3; Cl, 15.9%.

A solution of 3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (1.50 g), triethylamine (10 mL) and crude methyl 4-(aminomethyl)-2-hydroxybenzoate hydrochloride (3.46 g) in DMF (20 mL) was stirred at 20°C for 10 minutes, then cooled to 0°C. DEPC (98%, 1.47 mL) was added, then the mixture was stirred at 20°C for 17 hours. Workup and chromatography on silica gel, eluting with EtOAc:light petroleum (1:1) gave *N*-(3-hydroxy-4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph\{3\text{-OH, 4-COOMe}\}$] (1.40 g, 50%); mp (EtOAc/light petroleum) 132-133°C.
^{1}H NMR ($(CD_3)_2SO$): δ 10.76 (1H, br s, NH), 10.50 (1H, s, OH), 8.41 (1H, t, J = 5.8 Hz, $N\underline{H}CH_2$), 7.70 (1H, d, J = 8.1 Hz, ArH), 7.54 (1H, d, J = 7.8 Hz, ArH), 7.33 (1H, d, J = 8.1 Hz, ArH), 7.10 (1H, d, J = 2.2 Hz, H-2), 7.06 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 6.97 (1H, ddd, J = 7.8, 7.0, 0.8 Hz, ArH), 6.83 (1H, d,

J = 1.4 Hz, ArH), 6.74 (1H, dd, J = 8.2, 1.4 Hz, ArH), 4.27 (2H, d, J = 6.0 Hz, NHC$\underline{H}_2$), 3.88 (3H, s, OCH_3), 2.96, 2.54 (2x2H, 2xt, J = 7.7 Hz, 3-CH_2CH_2).
^{13}C NMR: δ 172.05 (s, CONH), 169.14 (s, $\underline{C}OOCH_3$), 160.10, 148.27, 136.22 (3xs, Ar), 129.92 (d, Ar), 126.98 (s, Ar), 122.14, 120.84, 118.30, 118.12, 118.09, 115.41 (6xd, Ar), 113.68 (s, Ar), 111.27 (d, Ar), 111.20 (s, Ar), 52.34 (q, OCH_3), 41.67 (t, $NHCH_2$), 36.23 (t, 3-$CH_2\underline{C}H_2$), 21.00 (t, 3-CH_2).
Analysis calculated for $C_{20}H_{20}N_2O_4$ requires:
C, 68.2; H, 5.7; N, 8.0%.
Found: C, 68.3; H, 5.9; N, 8.0%.

A solution of acetyl chloride (0.42 mL) in THF (5 mL) was added to a stirred solution of the above propanamide (1.22 g) and triethylamine (1.00 mL) in THF (15 mL) at 0°C, then the mixture was stirred at 20°C for 18 hours. The reaction was then quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). Evaporation and chromatography on silica gel, eluting with EtOAc:light petroleum (2:1) gave *N*-(3-acetoxy-4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide [II: R_1 = R_3 = H, R_2 = $(CH_2)_2CONHCH_2Ph$\{3-OAc, 4-COOMe\}] (1.28 g, 94%) as an oil.
^{1}H NMR ($CDCl_3$): δ 8.18 (1H, br s, NH), 7.87 (1H, d, J = 8.1 Hz, ArH), 7.57 (1H, d, J = 8.0 Hz, ArH), 7.31 (1H, dt, J = 8.1, 0.8 Hz, ArH), 7.17 (1H, ddd, J = 8.1, 7.0, 1.1 Hz, ArH), 7.09 (1H, ddd, J = 7.9, 7.0, 0.9 Hz, ArH), 6.97 (1H, dd, J = 8.1, 1.6 Hz, ArH), 6.84 (1H, d, J = 1.5 Hz, ArH), 6.77 (1H, d, J = 2.3 Hz, H-2), 5.67 (1H, br t, J = 5.8 Hz, N$\underline{H}CH_2$), 4.31 (2H, d, J = 6.0 Hz, NHC$\underline{H}_2$), 3.87 (3H, s, $COOCH_3$), 3.11, 2.58 (2x2H, 2xt, J = 6.9 Hz, 3-CH_2CH_2), 2.36 (3H, s, $OCOCH_3$).
^{13}C NMR: δ 172.84 (s, CONH), 170.14 (s, O$\underline{C}OCH_3$), 164.64 (s, $\underline{C}OOCH_3$), 150.82, 145.26, 136.33 (3xs, Ar),

132.04 (d, Ar), 126.85 (s, Ar), 125.42, 122.93, 122.31, 121.95 (4xd, Ar), 121.87 (s, Ar), 119.28, 118.52 (2xd, Ar), 114.08 (s, Ar), 111.36 (d, Ar), 52.23 (q, OCH_3), 42.62 (t, $NHCH_2$), 37.32 (t, 3-$CH_2\underline{C}H_2$), 21.46 (t, 3-CH_2), 21.06 (q, $OCO\underline{C}H_3$).

HREIMS *m/z* calculated for $C_{22}H_{22}N_2O_5$:
394.1529 (M^+).
Found: 394.1526.

The above *O*-acetate (1.47 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. Hydrolysis of the resulting oil with excess $KHCO_3$ in MeOH/water at 20°C for 1 hour (to remove the acetate group) gave an oil which was purified by chromatography on silica gel. Elution with EtOAc:light petroleum (1:2) gave firstly 2,2'-thiobis[*N*-(3-hydroxy-4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $(CH_2)_2CONHCH_2Ph${3-OAc, 4-COOMe}] (0.12 g, 9%); mp (MeOH/dilute HCl) 109-112°C (decomposed).

^1H NMR ($CDCl_3$): δ 10.50 (1H, s, OH), 10.17 (1H, s, NH), 7.49 (1H, d, *J* = 7.9 Hz, ArH), 7.31 (1H, d, *J* = 8.2 Hz, ArH), 7.19 (1H, d, *J* = 8.1 Hz, ArH), 7.07 (1H, ddd, *J* = 8.0, 7.1, 0.8 Hz, ArH), 6.97 (1H, ddd, *J* = 7.8, 7.2, 0.6 Hz, ArH), 6.32 (1H, d, *J* = 1.1 Hz, ArH), 5.98 (1H, dd, *J* = 8.2, 1.5 Hz, ArH), 5.72 (1H, t, *J* = 5.7 Hz, $N\underline{H}CH_2$), 4.22 (2H, d, *J* = 5.7 Hz, $NHC\underline{H}_2$), 3.86 (3H, s, OCH_3), 3.50, 2.88 (2x2H, 2xm, 3-CH_2CH_2).

^{13}C NMR: δ 173.77 (s, CONH), 170.06 (s, $\underline{C}OOCH_3$), 161.36, 145.57, 137.16 (3xs, Ar), 130.02 (d, Ar), 126.62, 125.16 (2xs, Ar), 122.69, 119.13, 118.43 (3xd, Ar), 117.65 (s, Ar), 117.40, 115.51, 111.53 (3xd, Ar), 111.07 (s, Ar), 52.18 (q, OCH_3), 43.19 (t, $NHCH_2$), 36.32 (t, 3-$CH_2\underline{C}H_2$), 21.22 (t, 3-CH_2).

Analysis calculated for $C_{40}H_{38}N_4O_8S$ requires:

C, 65.4; H, 5.2; N, 7.6; S, 4.4%.

Found: C, 65.2; H, 5.1; N, 7.4; S, 4.4%.

Elution with EtOAc:light petroleum (2:3) gave 2,2'-dithiobis[*N*-(3-hydroxy-4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide] (57) [V: n = 2; $R_1 = R_3$ = H, $R_2 = (CH_2)_2CONHCH_2Ph\{3\text{-OH, 4-COOMe}\}$] (0.38 g, 27%); mp (MeOH) 183-185°C.

^1H NMR ($CDCl_3$): δ 10.80 (1H, s, OH), 8.65 (1H, s, NH), 7.67 (1H, d, *J* = 8.1 Hz, ArH), 7.52 (1H, d, *J* = 8.0 Hz, ArH), 7.27 (1H, d, *J* = 7.7 Hz, ArH), 7.15 (1H, ddd, *J* = 8.1, 7.2, 0.9 Hz, ArH), 7.01 (1H, ddd, *J* = 7.9, 7.2, 0.7 Hz, ArH), 6.55 (1H, d, *J* = 1.5 Hz, ArH), 6.52 (1H, dd, *J* = 8.2, 1.5 Hz, ArH), 5.10 (1H, t, *J* = 5.9 Hz, $N\underline{H}CH_2$), 4.13 (2H, d, *J* = 6.0 Hz, $NHC\underline{H}_2$), 3.94 (3H, s, OCH_3), 2.88, 1.94 (2x2H, 2xt, *J* = 7.7 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 172.12 (s, CONH), 170.39 (s, $\underline{C}OOCH_3$), 161.55, 146.95, 137.29 (3xs, Ar), 130.09 (d, Ar), 127.01, 125.87 (2xs, Ar), 124.39 (d, Ar), 123.79 (s, Ar), 120.16, 119.86, 118.34, 115.69, 111.37 (5xd, Ar), 111.20 (s, Ar), 52.31 (q, OCH_3), 42.82 (t, $NHCH_2$), 37.09 (t, 3-$CH_2\underline{C}H_2$), 20.54 (t, 3-CH_2).

Analysis calculated for $C_{40}H_{38}N_4O_8S_2$ requires:

C, 62.7; H, 5.0; N, 7.3; S, 8.4%.

Found: C, 62.5; H, 4.9; N, 7.3; S, 8.4%.

Hydrolysis of 57 (0.28 g) with K_2CO_3 in MeOH/water at 50°C for 5 hours, under nitrogen as above, gave an oil. Chromatography on silica gel, eluting with EtOAc:light petroleum (1:1) containing 1% AcOH, gave 2,2'-dithiobis[*N*-(4-carboxy-3-hydroxybenzyl)-3-(3-indolyl)propanamide] (58) [VI: n = 2; $R_1 = R_3$ = H, $R_2 = (CH_2)_2CONHCH_2Ph\{3\text{-OH, 4-COOH}\}$] (72 mg, 27%); mp (MeOH/dilute HCl) 160-163.5°C (dec).

^1H NMR $(CD_3)_2SO$): δ 11.39 (1H, s, NH), 8.03 (1H, t, J = 5.9 Hz, N$\underline{H}$$CH_2$), 7.65 (1H, d, J = 8.1 Hz, ArH), 7.54 (1H, d, J = 8.0 Hz, ArH), 7.32 (1H, d, J = 8.2 Hz, ArH), 7.16 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 6.99 (1H, ddd, J = 7.8, 7.1, 0.7 Hz, ArH), 6.72 (1H, d, J = 1.3 Hz, ArH), 6.57 (1H, dd, J = 8.2, 1.4 Hz, ArH), 4.13 (2H, d, J = 5.9 Hz, NHC$\underline{H}_2$), 2.75, 2.24 (2x2H, 2xt, J = 7.8 Hz, 3-CH_2CH_2).

^{13}C NMR: δ 171.70 (s, CONH), 171.47 (s, COOH), 161.04, 147.83, 137.37 (3xs, Ar), 130.08 (d, Ar), 126.51, 125.11 (2xs, Ar), 123.25 (d, Ar), 122.42 (s, Ar), 119.49, 118.86, 117.73, 115.09, 111.41 (5xd, Ar), 111.21 (s, Ar), 41.67 (t, $NHCH_2$), 36.63 (t, 3-$CH_2\underline{C}H_2$), 20.41 (t, 3-CH_2).

Analysis calculated for $C_{38}H_{34}N_4O_8S_2 \cdot H_2O$ requires: C, 60.3; H, 4.8; N, 7.4; S, 8.5%.

Found: C, 60.2; H, 4.9; N, 7.1; S, 8.5%.

Compound 59 of Table 1

3-(3-Indolyl)propanoic acid [II: R_1 = R_3 = H, R_2 = $(CH_2)_2COOH$] (0.95 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above, to give crude 2,2'-dithiobis[3-(3-indolyl)propanoic acid] [VI: n = 2; R_1 = R_3 = H, R_2 = $(CH_2)_2COOH$] (1.12 g) as an oil. DEPC (98%, 1.00 mL) was added to a stirred solution of this oil, triethylamine (0.84 mL) and aniline (1.55 mL) in THF (15 mL) at 0°C, then the mixture was stirred at 20°C for 1 day. Dilute KOH (0.1 M, 100 mL) was added and the mixture stirred for 30 minutes (in an attempt to cleave the DEPC adduct and reform the disulfide), then the mixture extracted with CH_2Cl_2 (3 x 100 mL). Evaporation gave an oil which was partly purified by

chromatography on silica gel, eluting with EtOAc/light petroleum (2:1). The yellow disulfide was further purified by chromatography on fresh silica gel, eluting with CH_2Cl_2, then $CHCl_3$:EtOH (99:1), to give 2,2'-dithiobis[*N*-phenyl-3-(3-indolyl)propanamide] (59) [VI: n = 2; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHPh$] (0.23 g, 16% overall); mp (CH_2Cl_2/benzene) 181-182.5°C (an analytical sample recrystallized from CH_2Cl_2/light petroleum decomposed above 114°C).

^1H NMR ($(CD_3)_2CO$): δ 10.52 (1H, s, NH), 8.88 (1H, s, NHPh), 7.64 (1H, d, *J* = 8.0 Hz, ArH), 7.56 (2H, dd, *J* = 7.5, 0.9 Hz, ArH), 7.37 (1H, d, *J* = 8.2 Hz, ArH), 7.24 (2H, dd, *J* = 8.4, 7.5 Hz, ArH(Ph)), 7.16 (1H, ddd, *J* = 8.1, 7.1, 1.1 Hz, ArH), 7.02 (2H, m, ArH), 3.04, 2.54 (2x2H, 2xm, 3-CH_2CH_2).

^{13}C NMR: δ 171.48 (s, CONH), 140.24, 138.80 (2xs, Ar), 129.37 (2xd, Ar), 128.17, 126.81 (2xs, Ar) 124.57, 124.02 (2xd, Ar), 123.86 (s, Ar), 120.62, 120.36 (2xd, Ar), 120.23 (2xbr d, Ar), 112.38 (d, Ar), 38.97 (t,3-$CH_2\underline{C}H_2$) 21.39 (t, 3-CH_2).

Analysis calculated for $C_{34}H_{30}N_4O_2S_2 \cdot 0.5H_2O$ requires:
C, 68.1; H, 5.2; N, 9.4; S, 10.7%.
Found: C, 68.3; H, 5.1; N, 9.3; S, 10.9%.

<u>Compound 60 of Table 1</u>

DEPC (98%, 0.72 mL) was added to a stirred solution of DL-*N*-acetyltryptophan (1.00 g) and benzylamine (2.0 mL) in DMF (10 mL) at 0°C, then the mixture was stirred at 20°C for 16 hours. The reaction was then quenched with water and extracted with EtOAc. Evaporation gave an oil which was chromatographed on silica gel. Elution with CH_2Cl_2 and EtOAc gave firstly foreruns, then DL-α-acetylamino-*N*-benzyl-3-(3-indolyl)-propanamide [II: $R_1 = R_3 = H$,

R_2 = $CH_2CH(NHAc)CONHCH_2Ph$] (0.82 g, 60%); mp (CH_2Cl_2/light petroleum) 169-170°C.

^1H NMR (($(CD_3)_2SO$): δ 10.80 (1H, s, NH), 8.47 (1H, br t, J = 5.8 Hz, N$\underline{H}CH_2$), 8.08 (1H, d, J = 8.1 Hz, CHN$\underline{H}$), 7.61 (1H, d, J = 7.8 Hz, ArH), 7.33 (1H, d, J = 8.1 Hz, ArH), 7.26 (2H, dt, J = 7.1, 1.5 Hz, ArH), 7.20 (1H, dt, J = 7.2, 1.5 Hz, ArH), 7.13 (1H, m, H-2), 7.12 (2H, d, J = 7.2 Hz, ArH), 7.06 (1H, ddd, J = 7.9, 7.1, 0.9 Hz, ArH), 6.97 (1H, ddd, J = 7.9, 7.0, 0.9 Hz, ArH), 4.57 (1H, td, J = 8.3, 5.7 Hz, 3-$CH_2C\underline{H}$), 4.28, 4.24 (2x1H, 2xdd, J = 15.9, 5.9 Hz, $NHC\underline{H}_2$), 3.13 (1H, dd, J = 14.4, 5.6 Hz, 3-CH), 2.93 (1H, dd, J = 14.4, 8.6 Hz, 3-CH), 1.80 (3H, s, $COCH_3$).

^{13}C NMR: δ 171.59 (s, $COCH_3$), 169.02 (s, CONH), 139.18, 135.99 (2xs, Ar), 128.06 (d, 2C, Ar), 127.21 (s, Ar), 126.87 (d, 2C, Ar), 126.49, 123.47, 120.75, 118.39, 118.10, 111.17 (6xd, Ar), 110.11 (s, Ar), 53.53 (d, CH), 41.91 (t, $NHCH_2$), 27.92 (t, 3-CH_2), 22.50 (q, CH_3).

Analysis calculated for $C_{20}H_{21}N_3O_2$ requires:
C, 71.6; H, 6.3; N, 12.5%.
Found: C, 71.5; H, 6.4; N, 12.6%.

Acidification of the aqueous portion with dilute HCl, extraction with EtOAc and evaporation gave *N*-acetyltryptophan (0.30 g, 30%); mp (EtOAc/light petroleum) 204-206°C.

The above α-acetamide (1.25 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with $NaBH_4$ then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with CH_2Cl_2:EtOAc (2:1) to give firstly 2,2'-thiobis[α-acetylamino-*N*-benzyl-3-(3-indolyl)propanamide] [VI: n = 1; R_1 = R_3 = H, R_2 = $CH_2CH(NHAc)CONHCH_2Ph$] (0.30 g, 23%) as a mixture

of diastereoisomers; mp (EtOAc/light petroleum) 190-194°C.

^{1}H NMR ($(CD_3)_2SO$): δ 10.97, 10.94 (2x1H, 2xs, NH), 8.50, 8.48 (2x1H, 2xbr t, *J* = 5.8 Hz, N<u>H</u>CH_2), 8.17, 8.15 (2x1H, d, *J* = 8.4 Hz, CHN<u>H</u>), 7.63 (2x1H, d, *J* = 7.7 Hz, ArH), 7.3-6.9 (2x8H, m, ArH), 4.75 (2x1H, m, 3-CH_2C<u>H</u>), 4.27, 4.19 (4x1H, 2xdd, *J* = 16.1, 5.7 Hz, NHC$\underline{H}_2$), 3.44 (2x1H, m, 3-CH), 3.18 (2x1H, m, 3-CH), 1.79 (2x3H, 2xs, $COCH_3$).

^{13}C NMR: δ 171.20, 171.18 (2xs, <u>C</u>OCH_3), 169.13 (s, 2C, CONH), 138.83, 138.79 (2xs, Ar), 136.66 (s, 2C, Ar), 128.03, 128.01 (2xd, 2x2C, Ar), 127.42 (s, 2C, Ar), 126.96, 126.91 (2d, 2x2C, Ar), 126.51, 126.48 (2xd, Ar), 124.58, 124.55 (2xs, Ar), 121.97 (d, 2x2C, Ar), 119.02, 118.98 (2xd, Ar), 118.66 (d, 2C, Ar), 115.01, 114.94 (2xs, Ar), 110.79 (d, 2C, Ar), 53.66, 53.59 (2xd, 3-CH_2<u>C</u>H), 42.13 (t, 2C, $NHCH_2$), 28.14, 28.07 (2xt, 3-CH_2), 22.52 (q, 2C, CH_3).

Analysis calculated for $C_{40}H_{40}N_6O_4S \cdot 0.5H_2O$ requires:
C, 67.7; H, 5.8; N, 11.9; S, 4.5%.
Found: C, 67.7; H, 5.8; N, 11.9; S, 5.1%.

Elution with CH_2Cl_2:EtOAc (1:2) gave 2,2'-dithiobis[α-acetylamino-*N*-benzyl-3-(3-indolyl)-propanamide] (**60**) [VI: n = 2; R_1 = R_3 = H, R_2 = $CH_2CH(NHAc)CONHCH_2Ph$] (0.84 g, 62%) as a yellow oil (a mixture of diastereoisomers). Crystallizations from CH_2Cl_2/light petroleum gave a single pair of diastereoisomers; mp 140-144°C (dec).

^{1}H NMR ($CDCl_3$): δ 9.16 (1H, s, NH), 7.51 (1H, d, *J* = 8.1 Hz, ArH), 7.2-7.0 (6H, m, ArH), 6.89 (2H, m, ArH), 6.76 (1H, d, *J* = 7.2 Hz, CHN<u>H</u>), 6.16 (1H, t, *J* = 5.8 Hz, N<u>H</u>CH_2), 4.64 (1H, q, *J* = 7.2 Hz, 3-CH_2C<u>H</u>), 4.20, 4.12 (2x1H, 2xdd, *J* = 14.8, 5.9 Hz, NHC$\underline{H}_2$), 3.13

(1H, dd, J = 14.0, 7.1 Hz, 3-CH), 2.96 (1H, dd, J = 14.0, 7.3 Hz, 3-CH), 1.84 (3H, s, $COCH_3$).

Analysis calculated for $C_{40}H_{40}N_6O_4S_2 \cdot 0.5H_2O$ requires:
C, 64.8; H, 5.5; N, 11.3; S, 8.6 %.
Found: C, 65.0; H, 5.4; N, 11.3; S, 8.8%.

Crystallizations from EtOAc/light petroleum gave the other pair of diastereoisomers of **60**; mp 154.5-157.5°C (dec).

^{1}H NMR ($CDCl_3$): δ 9.27 (1H, s, NH), 7.42 (1H, d, J = 8.0 Hz, ArH), 7.28-7.12 (6H, m, ArH), 7.04 (1H, dd, J = 7.8, 7.0 Hz, ArH), 6.75 (2H, m, ArH), 6.45 (1H, br d, J = 7.1 Hz, CHN$\underline{H}$), 5.90 (1H, br s, N$\underline{H}CH_2$), 4.41 (1H, q, J = 7.4 Hz, 3-$CH_2C\underline{H}$), 4.17 (1H, dd, J = 14.8, 6.0 Hz, NHC$\underline{H}$), 4.08 (1H, dd, J =14.8, 5.0 Hz, NHC$\underline{H}$), 2.99 (1H, dd, J = 14.0, 6.9 Hz, 3-CH), 2.93 (1H, dd, J = 13.9, 7.6 Hz, 3-CH), 1.82 (3H, s, $COCH_3$).

^{13}C NMR: δ 170.74 (s, $\underline{C}OCH_3$), 169.92 (s, CONH), 137.42, 137.28 (2xs, Ar), 128.58 (d, 2C, Ar), 127.59 (s, Ar), 127.51 (d, 2C, Ar), 127.40 (d, Ar), 126.26 (s, Ar), 124.39, 120.37, 119.51 (3xd, Ar), 118.96 (s, Ar), 111.51 (d, Ar), 54.63 (d, 3-$CH_2\underline{C}H$), 43.70 (t, $NHCH_2$), 28.87 (t, 3-CH_2), 23.23 (q, CH_3).

Analysis calculated for $C_{40}H_{40}N_6O_4S_2$ requires:
C, 65.6; H, 5.5; N, 11.5; S, 8.7%.
Found: C, 65.4; H, 5.6; N, 11.5; S, 8.7%.

In DMSO solution, both pure diastereomers reverted to a 1:1 mixture of diastereoisomers by disulfide exchange within 3 minutes.

Compounds 61 and 62 of Table 1

Ethyl trifluoroacetate (1.7 mL) was added to a stirred solution of DL-tryptophan (2.3 g) and triethylamine (1.6 mL) in DMF (5 mL), then the flask was sealed and purged with nitrogen, and the mixture

stirred at 20°C for 1 day (method of Curphey TJ, J. Org. Chem. 1979;44:2805). Excess reagents were removed under vacuum, then triethylamine (1.9 mL) and DMF (10 mL) were added, and the mixture cooled to 0°C. DEPC (98%, 2.0 mL) was added, followed by benzylamine (1.72 mL), then the mixture was stirred under nitrogen at 20°C for 1 day. The resulting solution was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). Evaporation gave an oil which was purified by chromatography on silica gel, eluting with EtOAc:light petroleum (1:1), to give DL-*N*-benzyl-α-trifluoroacetylamino-3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(NHCOCF_3)CONHCH_2Ph$] (2.21 g, 50%); mp (EtOAc/light petroleum) 181-183°C.

^{1}H NMR ($(CD_3)_2SO$): δ 10.84 (1H, s, NH), 9.65 (1H, br s, CHN<u>H</u>), 8.79 (1H, t, J = 5.5 Hz, N<u>H</u>CH_2), 7.67 (1H, d, J = 7.8 Hz, ArH), 7.34 (1H, d, J = 8.0 Hz, ArH), 7.30 (2H, t, J = 7.2 Hz, ArH), 7.23 (1H, t, J = 7.3 Hz, ArH), 7.18 (2H, d, J = 7.5 Hz, ArH), 7.15 (1H, d, J = 2.2 Hz, H-2), 7.07 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 6.98 (1H, dd, J = 7.8, 7.0 Hz, ArH), 4.63 (1H, br m, 3-CH_2<u>C</u><u>H</u>), 4.32 (2H, d, J = 5.8 Hz, NHC<u>H</u>$_2$), 3.25 (1H, dd, J = 14.5, 5.0 Hz, 3-CH), 3.12 (1H, dd, J = 14.5, 9.9 Hz, 3-CH).

^{13}C NMR: δ 169.89 (s, CONH), 156.14, (q, J_{CF} = 36.5 Hz, <u>C</u>OCF_3), 138.92, 135.97 (2xs, Ar), 128.17, 126.95 (2xd, 2x2C, Ar), 126.95 (s, Ar) 126.68, 123.77, 120.86, 118.36, 118.17 (5xd, Ar), 115.69 (q, J_{CF} = 288 Hz, CF_3), 111.24 (d, Ar), 109.41 (s, Ar), 54.24 (d, 3-CH_2<u>C</u>H), 42.11 (t, $NHCH_2$), 27.08 (t, 3-CH_2).

Analysis calculated for $C_{20}H_{18}F_3N_3O_2$ requires:

C, 61.7; H, 4.6; N, 10.8%.

Found: C, 61.9; H, 4.9; N, 10.9%.

Acidification of the aqueous portion with dilute HCl, then extraction with EtOAc (3 x 100 mL) and evaporation gave DL-α-trifluoroacetylamino-3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(NHCOCF_3)COOH$] (0.72 g, 21%); mp (water) 155-157°C (Weygand F, Geiger R, Chem. Ber. 1956;89:647 record mp 162-163°C).

^{1}H NMR ($(CD_3)_2SO$): δ 10.86 (1H, br s, NH), 9.75 (1H, br d, J = 8.0 Hz, CHN<u>H</u>), 7.55 (1H, d, J = 7.8 Hz, ArH), 7.34 (1H, d, J = 8.1 Hz, ArH), 7.14 (1H, d, J = 2.3 Hz, H-2), 7.07 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 6.99 (1H, ddd, J = 7.9, 7.0, 0.9 Hz, ArH), 4.51 (1H, ddd, J = 10.2, 8.0, 4.2 Hz, 3-$CH_2C\underline{H}$), 3.32 (1H, dd, J = 14.8, 4.3 Hz, 3-CH), 3.17 (1H, dd, J = 14.8, 10.3 Hz, 3-CH).

^{13}C NMR: δ 171.64 (s, COOH), 156.23 (q, J_{CF} = 36.5 Hz, $\underline{C}OCF_3$), 136.01, 126.85 (2xs, Ar), 123.45, 120.93, 118.35, 117.90 (4xd, Ar), 117.09, 115.66 (q, J_{CF} = 288 Hz, CF_3), 111.36 (d, Ar), 109.56 (s, Ar), 53.58 (d, 3-$CH_2\underline{C}H$), 25.88 (t, 3-CH_2).

The above α-trifluoroacetamide (2.15 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was chromatographed directly on silica gel. Elution with CH_2Cl_2 and CH_2Cl_2:EtOAc (19:1) gave foreruns, including mono- and trisulfides, then 2,2′-dithiobis[*N*-benzyl-α-trifluoroacetylamino-3-(3-indolyl)propanamide] (61) [VI: n = 2; $R_1 = R_3 = H$, $R_2 = CH_2CH(NHCOCF_3)CONHCH_2Ph$] (1.01 g, 44%) as a yellow oil (a mixture of diastereoisomers). A subsample crystallized from EtOH was a single pair of diastereoisomers; mp 160-164°C (decomposed).

^{1}H NMR ($CDCl_3$): δ 8.76 (1H, s, NH), 7.57 (1H, d, J = 8.0 Hz, CHN<u>H</u>), 7.43 (1H, d, J = 7.9 Hz, ArH), 7.3-7.0 (6H, m, ArH), 6.75 (2H, m, ArH), 5.49 (1H, t,

J = 5.2 Hz, N$\underline{H}$CH$_2$), 4.26 (1H, td, J = 7.9, 6.4 Hz, 3-CH$_2$CH), 4.14 (1H, dd, J = 14.8, 5.8 Hz, NHCH$_2$), 4.00 (1H, dd, J = 14.5, 4.9 Hz, NHCH$_2$) 2.99 (1H, dd, J = 14.0, 8.4 Hz, 3-CH), 2.77 (1H, dd, J = 14.0, 5.9 Hz, 3-CH).

^{13}C NMR: δ 168.87 (s, CONH), 156.81 (q, J_{CF} = 36.5 Hz, $\underline{C}$OCF$_3$), 137.25, 136.61 (2xs, Ar), 128.73 (d, 2C, Ar), 127.71 (d, 3C, Ar), 126.96, 126.11 (2xs, Ar), 124.97, 120.95, 119.25 (3xd, Ar), 118.14 (s, Ar), 115.62 (q, J_{CF} = 288 Hz, CF$_3$), 111.49 (d, Ar), 54.67 (d, 3-CH$_2\underline{C}$H), 44.02 (t, NHCH$_2$), 28.22 (t, 3-CH$_2$).

Analysis calculated for $C_{40}H_{34}F_6N_6O_4S_2 \cdot 0.5H_2O$ requires:
C, 56.5; H, 4.1; N, 9.9; S, 7.5%.
Found: C, 56.6; H, 4.3; N, 9.8; S, 7.6%.

The trifluoroacetamide disulfide (61) (0.80 g) was treated with excess NaBH$_4$ at 20°C as above, then the resulting oil was chromatographed on alumina. Elution with CHCl$_3$:EtOH (99:1) gave foreruns, then elution with CHCl$_3$:EtOH (98:2) gave 2,2'-dithiobis[α-amino-*N*-benzyl-3-(3-indolyl)propanamide] (62) [VI: n = 2; R$_1$ = R$_3$ = H, R$_2$ = CH$_2$CH(NH$_2$)CONHCH$_2$Ph] (0.14 g, 22%); mp (CH$_2$Cl$_2$/light petroleum) 147-150°C (decomposed).

^{1}H NMR ((CD$_3$)$_2$SO): δ 11.56 (1H, s, NH), 8.18 (1H, t, J = 5.8 Hz, N$\underline{H}$CH$_2$), 7.61 (1H, d, J = 7.8 Hz, ArH), 7.36 (1H, d, J = 8.1 Hz, ArH), 7.33-6.95 (7H, m, ArH), 4.23, 4.13 (2x1H, 2xdd, J = 15.2, 5.8 Hz, NHC$\underline{H}_2$), 3.41 (1H, br m, 3-CH$_2$C$\underline{H}$), 2.93 (1H, dd, J = 13.7, 4.9 Hz, 3-CH), 2.64 (1H, br m, 3-CH), 1.7 (2H, br s, NH$_2$).

^{13}C NMR: δ 174.12 (s, CONH), 139.13, 137.38 (2xs, Ar), 128.06, 127.02 (2xd, 2x2C, Ar), 126.95, 126.71 (2xs, Ar), 126.51, 123.19, 119.62 (3xd, Ar), 119.18 (s, Ar), 118.87, 111.39 (2xd, Ar), 55.57 (d, 3-CH$_2\underline{C}$H), 41.90 (t, NHCH$_2$), 30.58 (t, 3-CH$_2$).

Analysis calculated for $C_{36}H_{36}N_6O_2S_2 \cdot 0.5H_2O$ requires:
C, 65.8; H, 5.6; N, 12.8%.
Found: C, 65.8; H, 5.8; N, 12.6%.

Compound 63 of Table 1

Acetyl chloride (0.50 mL, 7.0 mmol) was added to a stirred solution of DL-3-(3-indolyl)lactic acid (1.00 g, 14.3 mmol) and Et_3N (2 mL, 14.3 mmol) in THF (5 mL) at 0°C. The mixture was stirred at 0°C for 7 hours, then at 20°C for 15 hours, quenched with water (100 mL), acidified with dilute HCl (to pH 2), then extracted with EtOAc (3 x 100 mL). Evaporation gave crude (ca. 90% pure) DL-α-acetoxy-3-(3-indolyl)-propanoic acid [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(OAc)COOH$] (1.30 g) as an oil which was used directly.
^1H NMR ($(CD_3)_2SO$): δ 10.88 (1H, s, NH), 7.54 (1H, d, J = 7.8 Hz, ArH), 7.33 (1H, d, J = 8.0 Hz, ArH), 7.17 (1H, br s, H-2), 7.06 (1H, dd, J = 8.0, 7.1 Hz, ArH), 6.99 (1H, t, J = 7.4 Hz, ArH), 5.06 (1H, dd, J = 7.3, 4.9 Hz, 3-$CH_2C\underline{H}$), 3.22 (1H, dd, J = 15.1, 4.5 Hz, 3-CH), 3.16 (1H, dd, J = 15.0, 7.7 Hz, 3-CH), 2.00 (3H, s, $COCH_3$).
^{13}C NMR: δ 170.87, 169.96 (2xs, COOH, $O\underline{C}OCH_3$), 136.04, 127.28 (2xs, Ar), 123.84, 120.94, 118.43, 118.33, 111.39 (5xd, Ar), 108.90 (s, Ar), 72.70 (d, 3-$CH_2\underline{C}H$), 26.75 (t, 3-CH_2), 20.54 (q, CH_3).
HREIMS m/z calculated for $C_{13}H_{13}NO_4$:
247.0845 (M^+).
Found: 247.0848.

The above α-O-acetate (1.30 g of 90%, 4.4 mmol) and Et_3N (0.88 mL, 6.3 mmol) in DMF (10 mL) at 0°C was treated sequentially with DEPC (0.91 mL of 98%, 5.9 mmol) and benzylamine (0.69 mL, 6.3 mmol), and the mixture was stirred under nitrogen at 20°C for

18 hours. Workup and chromatography on silica gel, eluting with EtOAc/light petroleum (1:2 then 1:1) gave DL-α-acetoxy-*N*-benzyl-3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(OAc)CONHCH_2Ph$] (0.29 g, 18%) as an oil.

^{1}H NMR ($CDCl_3$): δ 8.05 (1H, s, NH), 7.60 (1H, d, *J* = 7.9 Hz, ArH), 7.37 (1H, dt, *J* = 8.1, 0.9 Hz, ArH), 7.26-7.21 (3H, m, ArH), 7.20 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz, ArH), 7.12 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, ArH), 6.97 (1H, d, *J* = 2.4 Hz, H-2), 6.94 (2H, m, ArH), 6.07 (1H, t, *J* = 5.8 Hz, N$\underline{H}$CH$_2$), 5.47 (1H, t, *J* = 5.4 Hz, 3-CH$_2$C$\underline{H}$), 4.38 (1H, dd, *J* = 14.9, 6.1 Hz, NHC$\underline{H}$), 4.29 (1H, dd, *J* = 14.9, 5.5 Hz, NHC$\underline{H}$), 3.41 (2H, d, *J* = 5.5 Hz, 3-CH$_2$), 2.06 (3H, s, COCH$_3$).

^{13}C NMR: δ 169.63, 169.33 (2xs, CONH, O$\underline{C}$OCH$_3$), 137.56, 136.05 (2xs, Ar), 128.55 (d, 2C, Ar), 127.75 (s, Ar), 127.60 (d, 2C, Ar), 127.40, 123.43, 122.08, 119.61, 118.92, 111.13 (6xd, Ar), 109.83 (s, Ar), 74.56 (d, 3-CH$_2\underline{C}$H), 43.12 (t, NHCH$_2$), 27.42 (t, 3-CH$_2$), 21.09 (q, CH$_3$).

HREIMS *m/z* calculated for $C_{20}H_{20}N_2O_3$:
336.1474 (M^+).
Found: 336.1471.

Unreacted α-acetoxy-3-(3-indolyl)propanoic acid (0.68 g, 52%) was also recovered.

Alternative Preparation of Above Acetoxypropanamide

A solution of $SnCl_4$ (5.4 mL, 46 mmol) in CCl_4 (50 mL) was added dropwise to a stirred solution of indole (5.4 g, 46 mmol) and *N*-benzyl-2,3-epoxypropanamide (Dolzani L, Tamaro M, Monti-Bragadin C, Cavicchionz G, Vecchiati G, D'Angeli F, Mutation Res. 1986;172:37) (14 g of 85%, 67 mmol) in CCl_4 (100 mL) at -5°C (method of

Entzeroth M, Kunczik T, Jaenicke L, Liebig's Ann. Chim. 1983:226). The mixture was stirred at 20°C for 16 hours, then diluted with $CHCl_3$ (100 mL) and 10% $NaHCO_3$ (250 mL) and stirred vigorously for 4 hours. The aqueous portion was separated and extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were washed with water, dried, and the solvents removed. The resulting oil was chromatographed on silica gel, eluting with CH_2Cl_2/light petroleum (1:1) to yield unreacted indole (1.27 g, 24%). Elution with CH_2Cl_2 gave mixtures, then CH_2Cl_2/EtOAc (4:1) gave a crude product. This was crystallized successively from CH_2Cl_2/light petroleum, then CH_2Cl_2/benzene/light petroleum to give DL-*N*-benzyl-α-hydroxy-3-(3-indolyl)-propanamide [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(OH)CONHCH_2Ph$] (0.70 g, 5%); mp 127-128.5°C.

^{1}H NMR ($(CD_3)_2SO$): δ 10.79 (1H, s, NH), 8.20 (1H, t, J = 6.2 Hz, N$\underline{H}$CH$_2$), 7.56 (1H, d, J = 7.8 Hz, ArH), 7.34 (1H, d, J = 8.1 Hz, ArH), 7.24 (2H, m, ArH), 7.19 (1H, m, ArH), 7.12 (1H, d, J = 2.3 Hz, H-2), 7.10 (1H, m, ArH), 7.05 (1H, ddd, J = 8.0, 7.0, 1.0 Hz, ArH), 6.96 (1H, ddd, J = 7.9, 7.0, 0.9 Hz, ArH), 5.54 (1H, d, J = 5.7 Hz, OH), 4.26 (2H, d, J = 6.2 Hz, NHC$\underline{H}_2$), 4.19 (1H, ddd, J = 7.5, 5.7, 4.3 Hz, 3-CH$_2$C$\underline{H}$), 3.14 (1H, dd, J = 14.5, 4.1 Hz, 3-CH), 2.91 (1H, dd, J = 14.5, 7.6 Hz, 3-CH).

^{13}C NMR: δ 173.59 (s, CONH), 139.40, 135.93 (2xs, Ar), 128.00 (d, 2C, Ar), 127.60 (s, Ar), 126.95 (d, 2C, Ar), 126.42, 123.58, 120.56, 118.60, 117.97, 111.05 (6xd, Ar), 110.53 (s, Ar), 71.86 (d, 3-CH$_2$$\underline{C}$H), 41.60 (t, NHCH$_2$), 30.33 (t, 3-CH$_2$).

Analysis calculated for $C_{18}H_{18}N_2O_2 \cdot 0.25H_2O$ requires:
C, 72.4; H, 6.2; N, 9.4%.
Found: C, 72.4; H, 6.0; N, 9.3%.

This α-hydroxypropanamide (0.62 g, 2.1 mmol) was stirred with pyridine (1.5 mL, 18.5 mmol) and Ac_2O (1.7 mL, 18.0 mmol) at 20°C for 17 hours. The mixture was partitioned between water and CH_2Cl_2, and worked up to give a quantitative yield of DL-α-acetoxy-*N*-benzyl-3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(OAc)CONHCH_2Ph$].

This compound (1.07 g) was treated with S_2Cl_2 as above, and the resulting product mixture chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (19:1), to give firstly 2,2'-thiobis-[α-acetoxy-*N*-benzyl-3-(3-indolyl)propanamide] [VI: $n = 1$, $R_1 = R_3 = H$, $R_2 = CH_2CH(OAc)CONHCH_2Ph$] (0.19 g, 17%) as a mixture of diastereoisomers; mp (MeOH/dilute HCl) 105-109°C.
^{1}H NMR ($CDCl_3$): δ 10.09, 10.06 (2x1H, 2xs, NH), 7.61, 7.60 (2x1H, 2xd, J = 7.9 Hz, ArH), 7.24 (2x1H, d, J = 8.2 Hz, ArH), 7.14-7.00 (2x5H, m, ArH), 6.78, 6.70 (2x2H, 2xm, ArH), 6.27, 6.26 (2x1H, 2xt, J = 5.8 Hz, $N\underline{H}CH_2$), 5.72 (1H, dd, J = 7.0, 6.0 Hz, 3-$CH_2C\underline{H}$), 5.69 (1H, t, J = 6.1 Hz, 3-$CH_2C\underline{H}$), 4.30, 4.27 (2x1H, 2xdd, J = 15.0, 5.8 Hz, $NHC\underline{H}$), 4.23, 4.21 (2x1H, 2xdd, J = 15.0, 5.4 Hz, $NHC\underline{H}$), 3.67 (1H, dd, J = 14.5, 7.0 Hz, 3-CH), 3.65 (1H, dd, J = 14.7, 5.8 Hz, 3-CH), 3.60 (1H, dd, J = 14.7, 6.3 Hz, 3-CH), 3.53 (1H, dd, J = 14.5, 6.0 Hz, 3-CH) 2.12, 2.11 (2x3H, 2xs, $COCH_3$).
^{13}C NMR ($CDCl_3$): δ 169.87, 169.73 (2xs, 2x2C, $COCH_3$, CONH), 137.09, 137.03, 136.70, 136.65 (4xs, Ar), 128.60, 128.56 (2xd, 2x2C, Ar), 127.48, 127.44 (2xd, Ar), 127.43, 127.39 (2xs, Ar), 127.31, 127.28 (2xd, 2x2C, Ar), 125.47, 125.40 (2xs, Ar), 122.95, 122.93 (2xd, Ar), 119.64 (d, 2C, Ar), 119.07, 118.88 (2xd, Ar), 113.92, 113.70 (2xs, Ar), 111.32 (d, 2C, Ar),

73.99, 73.77 (2xd, 3-$CH_2\underline{C}H$), 43.31 (t, 2C, $NHCH_2$), 28.00 (t, 2C, 3-CH_2), 21.19, 21.13 (2xq, CH_3).
Analysis calculated for $C_{40}H_{38}N_4O_2S$) requires:
C, 68.4; H, 5.4; N, 8.0; S, 4.6%.
Found: C, 68.2; H, 5.6; N, 8.0; S, 4.8%.

Elution with CH_2Cl_2/EtOAc (9:1) gave 2,2'-dithiobis[α-acetoxy-*N*-benzyl-3-(3-indolyl)-propanamide] (**63**) [VI: n = 2, R_1 = R_3 = H, R_2 = $CH_2CH(OAc)CONHCH_2Ph$] (0.76 g, 65%) as a yellow oil (mixture of diastereoisomers). A subsample crystallized from CH_2Cl_2/dilute HCl as a single pair of diastereoisomers; mp 120-124°C (dec).
^1H NMR ($CDCl_3$): δ 8.64 (1H, s, NH), 7.60 (1H, d, *J* = 7.9 Hz, ArH), 7.27-7.15 (4H, m, ArH), 7.12, 7.11 (2x1H, 2xt, *J* = 8.1 Hz, ArH), 6.91 (2H, m, ArH), 6.12 (1H, t, *J* = 5.6 Hz, $N\underline{H}CH_2$), 5.41 (1H, t, *J* = 6.2 Hz, 3-$CH_2C\underline{H}$), 4.30, 4.24 (2x1H, 2xdd, *J* = 14.8, 5.71 Hz, $NHC\underline{H}_2$), 3.31 (1H, dd, *J* = 14.5, 5.8 Hz, 3-CH), 3.17 (1H, dd, *J* = 14.5, 6.6 Hz, 3-CH), 1.99 (3H, s, $COCH_3$).
^{13}C NMR ($CDCl_3$): δ 169.65, 168.96 (2xs, CONH, $\underline{C}OCH_3$), 137.50, 137.05 (2xs, Ar), 128.63 (d, 2C, Ar), 127.81 (s, Ar), 127.68 (d, 2C, Ar), 127.49 (d, Ar), 126.85 (s, Ar), 124.30, 120.30, 120.03 (3xd, Ar), 117.87 (s, Ar), 111.33 (d, Ar), 74.06 (d, 3-$CH_2\underline{C}H$), 43.30 (t, $NHCH_2$), 27.45 (t, 3-CH_2), 21.18 (q, CH_3).
Analysis calculated for $C_{40}H_{38}N_4O_2S_2$ requires:
C, 65.4; H, 5.2; N, 7.6; S, 8.7%.
Found: C, 65.2; H, 5.2, N, 7.8; S, 8.8%.

Compound **64** of Table 1

Hydrolysis of **63** with excess $KHCO_3$ in aqueous MeOH at 20°C for 2 hours gave 2,2'-dithiobis[α-hydroxy-N-(phenylmethyl)-1H-indole-3-propanamide] (**64**) [II: R_1 = R_3 = H, R_2 = $Ch_2CH(OH)COOH$] as an oil

(mixture of diastereomers) in essentially quantitative yield. Crystallization from CH_2Cl_2/light petroleum gave a single pair of diastereomers (66% yield); mp 120-125°C.

^1H NMR ($CDCl_3$): δ 7.61 (1H, d, J = 8.0 Hz, ArH), 7.33-7.17 (5H, m, ArH), 7.12 (2H, dd, J = 7.8, 1.5 Hz, ArH), 7.09 (1H, ddd, J = 8.1, 5.4, 2.7 Hz, ArH), 6.80 (1H, t, J = 5.8 Hz, N*H*CH_2), 4.33, 4.27 (2x1H, 2xdd, J = 14.8, 5.9 Hz, NHC*H*$_2$), 3.78 (1H, ddd, J = 9.5, 5.4, 3.4 Hz, 3-CH_2C*H*), 3.30 (1H, d, J = 5.4 Hz, OH), 3.24 (1H, dd, J = 14.4, 3.4 Hz, 3-CH), 2.88 (1H, dd, J = 14.3, 9.5 Hz, 3-CH).

Analysis calculated for $C_{36}H_{34}N_4O_4S_2$ requires:

C, 66.1; H, 5.3; N, 8.6; S, 9.6%.

Found: C, 66.5; H, 5.2; N, 8.6; S, 9.8%

EXAMPLE C

Preparation of Compounds 5 and 33 of Table 1 by the Method Outlined in Scheme 3

1-Methyl-2-indolinone [VII: R_1 = H, R_3 = Me] was condensed with diethyl oxalate in NaOEt/EtOH, to give ethyl 1-methyl isatylidenehydroxyacetate [VIII: R_1 = H, R_3 = Me, R = COOEt] (82% yield); mp 62-64°C (according to the method of Porter JC, Robinson R, Wyler M, J. Chem. Soc. 1941:620, who report mp 81°C). The above acetate [VIII: R_1 = H, R_3 = Me, R = COOEt] (2.30 g) was hydrogenated in glacial AcOH (150 mL) containing concentrated H_2SO_4 (1 mL) and 5% Pd/C catalyst (5 g) for 1 day. The reaction mixture was filtered onto NaOAc (4 g) and the solvent removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and water, then the aqueous phase re-extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with water, the solvent removed, and

the residue was chromatographed on silica gel. Elution with CH_2Cl_2 gave ethyl 2-(1-methyl-2-oxo-3-indolinyl)-acetate [III: R_1 = H, R_2 = CH_2COOEt, R_3 = Me] as an oil (1.23 g, 57%).

^{1}H NMR ($CDCl_3$): δ 7.29 (1H, t, J = 7.7 Hz, ArH), 7.26 (1H, d, J = 7.5 Hz, ArH), 7.03 (1H, t, J = 7.5 Hz, ArH), 6.84 (1H, d, J = 7.7 Hz, ArH), 4.15, 4.11 (2x1H, 2xdq, J = 10.8, 7.1 Hz, $COOCH_2$), 3.79 (1H, dd, J = 8.0, 4.4 Hz, H-3), 3.23 (3H, s, NCH_3), 3.07 (1H, dd, J = 16.8, 4.4 Hz, CH_2CO), 2.78 (1H, dd, J = 16.8, 8.1 Hz, CH_2CO), 1.20 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$): δ 176.72 (s, $\underline{C}ONCH_3$), 171.02 ($\underline{C}OOCH_2$) 144.35 (s, ArH), 128.27 (d, ArH), 128.18 (s, ArH), 123.80, 122.45, 108.01 (3xd, ArH), 60.85 (t, OCH_2), 41.83 (d, C-3), 34.94 (t, $\underline{C}H_2CO$), 26.28 (q, NCH_3), 14.05 (q, $OCH_2\underline{C}H_3$).

The above oxoacetate [III: R_1 = H, R_2 = CH_2COOEt, R_3 = Me] was treated with P_2S_5 as described in Example A, then chromatographed on silica gel, with CH_2Cl_2/light petroleum (3:2) eluting ethyl 2-(1-methyl-2-thioxo-3-indolinyl)acetate [IV: R_1 = H, R_2 = CH_2COOEt, R_3 = Me] (5) (90% yield); mp (benzene/light petroleum) 47-48°C.

^{1}H NMR ($CDCl_3$): δ 7.35 (2H, m, ArH), 7.16 (1H, td, J = 7.5, 0.8 Hz, ArH), 7.01 (1H, dd, J = 7.7, 1.0 Hz, ArH), 4.15 (2H, q, J = 7.1 Hz, $COOCH_2$), 4.14 (1H, m, H-3), 3.65 (3H, s, NCH_3), 3.39 (1H, dd, J = 17.0, 4.1 Hz, CH_2CO), 2.83 (1H, dd, J = 17.0, 8.6 Hz, CH_2CO), 1.22 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$): δ 204.35 (s, $\underline{C}SNCH_3$), 171.11 (s, $\underline{C}OOCH_2$), 145.73, 133.01 (2xs, ArH), 128.39, 124.34, 123.94, 109.46 (4xd, ArH), 60.85 (t, OCH_2), 53.44 (d, C-3), 38.66 (t, $\underline{C}H_2CO$), 31.52 (q, NCH_3), 14.13 (q, $OCH_2\underline{C}H_3$).

Analysis calculated for $C_{13}H_{15}NO_2S$ requires:

C, 62.7; H, 6.0; N, 5.6; S, 12.9%.

Found: C, 62.5; H, 6.2; N, 5.6; S, 12.8%.

A solution of crude 5 in EtOH was exposed to air for 2 weeks, during which time bis[ethyl 1-methylindolyl-3-acetate-(2)]disulfide [V: R_1 = H, R_2 = CH_2COOEt, R_3 = Me] (33) slowly separated as yellow needles (0.18 g, 26%); mp 117-119°C.

^{1}H NMR ($CDCl_3$): δ 7.53 (1H, dt, J = 8.0, 0.8 Hz, ArH), 7.30 (1H, ddd, J = 8.3, 6.3, 1.1 Hz, ArH), 7.27 (1H, ddd, J = 8.1, 1.6, 0.7 Hz, ArH), 7.12 (1H, ddd, J = 8.0, 6.2, 1.8 Hz, ArH), 3.96 (2H, q, J = 7.1 Hz, $COOCH_2$), 3.54 (3H, s, NCH_3), 3.38 (2H, s, CH_2CO), 1.14 (3H, t, J = 7.1 Hz, $OCH_2\underline{C}\underline{H}_3$).

^{13}C NMR ($CDCl_3$): δ 171.06 (s, $\underline{C}OOCH_2$), 138.45, 128.42, 126.47 (3xs, ArH), 124.33, 120.20, 120.07 (3xd, ArH), 117.59 (s, ArH), 109.93 (d, ArH), 60.70 (t, OCH_2), 30.99 (t, $\underline{C}H_2CO$), 29.97 (q, NCH_3), 14.13 (q, $OCH_2\underline{C}H_3$).

Analysis calculated for $C_{26}H_{28}N_2O_4S_2$ requires:

C, 62.9; H, 5.7; N, 5.7; S, 12.9%.

Found: C, 62.7; H, 5.6; N, 5.6; S, 13.0%.

<u>Compounds 10 and 38 of Table 1</u>

Similar reactions on 2-indolinone [VII: R_1 = R_3 = H], using diethyl malonate, gave ethyl 3-(2-oxo-3-indolinyl)propanoate [III: R_1 = R_3 = H, R_2 = $(CH_2)_2COOE$] (Julian PL, Printy HC, <u>J. Am. Chem. Soc.</u> 1953;75:5301). Reaction of this with P_2S_5 as described in Example A, followed by chromatography on silica gel, elution with CH_2Cl_2, and crystallization from benzene/light petroleum over 2 days, gave bis[ethyl indolyl-3-propanoate-(2)]disulfide [V: R_1 = R_3 = H, R_2 = $(CH_2)_2COOEt$] (38) (18% yield); mp 137-139°C.

^{1}H NMR ($CDCl_3$): δ 8.25 (1H, s, NH), 7.55 (1H, d, J = 8.0 Hz, ArH), 7.22 (2H, m, ArH), 7.11 (1H, ddd, J = 8.0, 5.0, 3.0 Hz, ArH), 4.02 (2H, q, J = 7.1 Hz, $COOCH_2$), 2.98, 2.46 (2x2H, 2xt, J = 7.9 Hz, CH_2CH_2CO), 1.16 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).
^{13}C NMR ($CDCl_3$): δ 173.03 (s, $\underline{C}OOCH_2$), 137.26, 127.22, 125.83 (3xs, ArH), 124.26 (d, ArH), 122.81 (s, ArH), 120.03, 119.63, 111.19 (3xd, ArH), 60.41 (t, $COO\underline{C}H_2$), 35.20 (t, CH_2CO), 20.26 (t, 3-CH_2), 14.14 (q, $OCH_2\underline{C}H_3$).
Analysis calculated for $C_{26}H_{28}N_2O_4S_2$ requires:
C, 62.9; H, 5.7; N, 5.6; S, 12.9%.
Found: C, 63.3; H, 5.9; N, 5.7; S, 13.0%.

Treatment of the mother liquors with $NaBH_4$ gave ethyl 3-(2-thioxo-3-indolinyl)propanoate [IV: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOEt$] (10) (56% yield) as an oil.
^{1}H NMR ($CDCl_3$): δ 10.40 (1H, s, NH), 7.31 (1H, d, J = 7.4 Hz, ArH), 7.27 (1H, td, J = 7.8, 0.7 Hz, ArH), 7.14 (1H, td, J = 7.5, 0.7 Hz, ArH), 7.01 (1H, d, J = 7.8 Hz, ArH), 4.07, 4.03 (2x1H, 2xdq, J = 10.8, 7.1 Hz, $COOCH_2$), 3.91 (1H, t, J = 5.4 Hz, H-3), 2.52 (2H, m, $C\underline{H}_2CH_2CO$), 2.41 (1H, ddd, J = 15.8, 9.9, 5.9 Hz, CH_2CO), 2.10 (1H, ddd, J = 15.8, 9.1, 6.7 Hz, CH_2CO), 1.20 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).
^{13}C NMR ($CDCl_3$): δ 207.31 (s, CSNH), 172.96 (s, $\underline{C}OOCH_2$), 143.31, 133.15 (2xs, ArH), 128.40, 124.34, 124.07, 110.04 (4xd, ArH), 60.55 (t, OCH_2), 56.44 (d, C-3), 29.56, 28.16 (2xt, $(CH_2)_2CO$), 14.15 (q, OCH_2CH_3).
Analysis calculated for $C_{13}H_{15}NO_2S$ requires:
C, 62.6; H, 6.1; N, 5.6; S, 12.9%.
Found: C, 62.3; H, 5.9; N, 5.6; S, 12.6%.

Compounds 12 of Table 1

Similar treatment of 1-methyl-2-indolinone, using diethyl malonate, and subsequent thiation, gave ethyl 3-(1-methyl-2-thioxo-3-indolinyl)propanoate [IV: R_1 = H, R_2 = $(CH_2)_2COOEt$, R_3 = Me] (**12**); mp (benzene/light petroleum) 61-63°C.

^1H NMR ($CDCl_3$): δ 7.35 (2H, m, ArH), 7.20 (1H, t, J = 7.5 Hz, ArH), 7.00 (1H, d, J = 7.8 Hz, ArH), 4.05, 4.02 (2x1H, 2xdq, J = 10.8, 7.1 Hz, $COOCH_2$), 3.92 (1H, t, J = 5.4 Hz, H-3), 3.63 (3H, s, NCH_3), 2.53 (2H, td, J = 8.0, 5.4 Hz, $C\underline{H}_2CH_2CO$), 2.32, 2.01 (2x1H, 2xtd, J = 16.0, 8.0 Hz, $CH_2C\underline{H}_2CO$), 1.19 (3H, t, J = 7.1 Hz, $CH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$): δ 204.85 (s, $\underline{C}SNCH_3$), 172.87 (s, $\underline{C}OOCH_2$), 145.89, 132.44 (2xs, ArH), 128.37, 124.30, 124.00, 109.49 (4xd, ArH), 60.43 (t, OCH_2), 56.29 (d, C3), 31.35 (q, NCH_3), 29.53, 28.46 (2xt, CH_3CH_2CO), 14.15 (q, $OCH_2\underline{C}H_3$).

Analysis calculated for $C_{14}H_{17}NO_2S$ requires:
C, 63.9; H, 6.5; N, 5.3; S, 12.2%.
Found: C, 64.1; H, 6.7; N, 5.4; S, 12.0%.

Compounds 41 and 42 of Table 1

Similar treatment of 5-methyl-2-indolinone [VII: R_1 = 5-Me, R_3 = H] gave bis[ethyl 5-methylindolyl-3-propanoate-(2)]disulfide [V: R_1 = 5-Me, R_2 = $(CH_2)_2COOEt$, R_3 = H] (**42**) as a yellow solid; mp (benzene/petroleum ether) 138.5-139°C.

^1H NMR ($CDCl_3$): 8.10 (1H, s, NH), 7.32 (1H, d, J = 0.6 Hz, H-4), 7.15 (1H, d, J = 8.3 Hz, H-7), 7.06 (1H, dd, J = 8.3, 1.4 Hz, H-6), 4.03 (2H, q, J = 7.2 Hz, $C\underline{H}_2CH_3$), 3.02-2.85 (2H, m, $CH_2CH_2CO_2$), 2.51-2.36 (2H, m, $CH_2CH_2CO_2$), 2.43 (3H, s, $ArCH_3$), 1.18 (3H, t, J = 7.2 Hz, $CH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$): δ 173.1 (CO_2Et), 135.6, 129.3, 127.4, 125.9, 122.3 (C-2,3,5,8,9), 126.0, 119.1, 110.9 (C-4,6,7), 60.4 ($O\underline{C}H_2CH_3$), 35.2 ($\underline{C}H_2CH_2CO2$), 21.5 ($ArCH_3$), 20.3 ($CH_2\underline{C}H_2CO2$), 14.1 ($OCH_2\underline{C}H_3$).

Analysis calculated for $C_{28}H_{32}N_2O_4S_2 \cdot 0.5C_6H_6$ requires:
C, 66.1; H, 6.3; N, 5.0; S, 11.4%.
Found: C, 66.2; H, 6.4; N, 5.0; S, 11.7%.

Ester hydrolysis of **42** as above gave bis[5-methylindolyl-3-propanoic acid-(2)]disulfide [V: R_1 = 5-Me, R_2 = $(CH)_2CO_2H$, R_3 = H] (**41**) as orange-brown prisms; mp (CH_2Cl_2/petroleum ether) 91.5-95°C.

^1H NMR ($CDCl_3$): δ 7.98 (1H, s, NH), 7.33 (1H, s, H-4), 7.14 (1H, d, J = 8.4 Hz, H-7), 7.07 (1H, dd, J = 8.4, 1.3 Hz, H-6), 2.98 (2H, t, J = 7.5 Hz, $CH_2CH_2CO_2$), 2.56 (2H, t, J = 7.5 Hz, $CH_2CH_2CO_2$), 2.43 (3H, s, $ArCH_3$).

HREIMS m/z calculated for $C_{24}H_{24}N_2O_4S_2$ requires:
235.06670.
Found: m/z 235.06639.

<u>Compounds **43** and **44** of Table 1</u>

Similar treatment of 6-methyl-2-indolinone [VII: R_1 = 6-Me, R_3 = H] gave bis[ethyl 6-methylindolyl-3-propanoate-(2)]disulfide [V: R_1 = 6-Me, R_2 = $(CH_2)_2COOEt$, R_3 = H] (**44**) as a yellow solid; mp 122-123.5°C.

^1H NMR ($CDCl_3$): δ 8.06 (1H, s, NH), 7.43 (1H, d, J = 8.2 Hz, H-4), 7.03-7.00 (1H, m, H-7), 6.97-6.92 (1H, m, H-5), 4.02 (2H, q, J = 7.2 Hz, $C\underline{H}_2CH_3$), 2.98-2.91 (2H, m, CH_2CH_2CO), 2.48-2.42 (2H, m, CH_2CH_2CO), 2.44 (3H, s, ArHMe), 1.17 (3H, t, J = 7.2 Hz, $CH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$): δ 173.0 (CO_2Et), 137.7, 134.3, 125.2, 125.0, 122.9 (C-2,3,6,8,9), 121.9, 119.3 (C-4,5,7),

60.3 (OCH_2CH_3), 35.2 ($CH_2CH_2CO_2$), 21.8 ($ArCH_3$), 20.3 ($CH_2CH_2CO_2$), 14.1 (OCH_2CH_3).

Analysis calculated for $C_{28}H_{32}N_2O_4S_2$ requires:

C, 64.1; H, 6.2; N, 5.3; S, 12.2%.

Found: C, 64.1; H, 6.2; N, 5.4; S, 12.0%.

Ester hydrolysis of the above as above gave bis[methylindolyl-3-propanoate-(2)]disulfide [V: R_1 = 6-Me, R_2 = $(CH_2)_2COOEt$, R_3 = H] (43) as yellow microcrystals; mp (CH_2Cl_2/petroleum ether) 126-128°C.

^{1}H NMR ($(CD3)_2CO$): δ 10.34 (1H, br s, NH), 7.49 (1H, d, J = 8.2 Hz, H-4), 7.19 (H, s, H-7), 6.19 (1H, dd, J = 8.2, 1.2 Hz, H-5), 2.97-2.90 (2H, m, $CHCH_2CO_2$), 2.49-2.43 (2H, m, $CH_2CH_2CO_2$), 2.42 (3H, s, $ArCH_3$).

Analysis calculated for $C_{24}H_{24}N_2O_4S_2 \cdot H_2O$ requires:

C, 60.4; H, 5.9; N, 5.9%.

Found: C, 60.2; H, 5.3; N, 5.9%.

<u>Compounds 45 and 46 of Table 1</u>

Similar treatment of 7-methyl-2-indolinone [VII: R_1 = 7-Me, R_3 = H] gave bis[ethyl 7-methylindolyl-3-propanoate-(2)]disulfide [V: R_1 = 7-Me, R_2 = $(CH_2)_2COOEt$, R_3 = H] (46) as a yellow solid; mp (benzene/petroleum ether) 120-122.5°C.

^{1}H NMR ($CDCl_3$): δ 8.23 (1H, s, NH), 7.38 (1H, d, J = 7.4 Hz, ArH), 7.00 (1H, t, J = 7.3 Hz, H-5), 6.94 (1H, d, J = 6.3 Hz, ArH), 4.02 (2H, q, J = 7.2 Hz, CH_2CH_3), 3.16 (2H, t, J = 7.5 Hz, $CH_2CH_2CO_2$), 2.71 (2H, t, J = 7.5 Hz, $CH_2CH_2CO_2$), 1.96 (3H, s, $ArCH_3$), 1.23 (3H, t, J = 7.2 Hz, CH_2CH_3).

^{13}C NMR ($CDCl_3$): δ 173.6 (CO_2Et), 136.9, 127.0, 124.8, 122.9, 121.0 (C-2,3,7,8,9), 124.3, 120.0, 117.0 (C-4,5,6), 60.6 (OCH_2CH_3), 35.3 ($CH_2CH_2CO_2$), 20.9 ($CH_2CH_2CO_2$), 16.0 ($ArCH_3$), 14.1 (OCH_2CH_3).

Analysis calculated for $C_{28}H_{32}N_2O_4S_2$ requires:

C, 64.1; H, 6.2; N, 5.3; S, 12.2%.

Found: C, 64.2; H, 6.4; N, 5.4; S, 12.0%.

Ester hydrolysis of **46** as above gave bis[7-methylindolyl-3-propanoic acid-(2)]disulfide [V: R_1 = 7-Me, R_2 = $(CH_2)_2CO2H$, R_3 = H] (**45**) as green needles; mp (AcOH/petroleum ether) 172.5-175°C. ^1H NMR ($(CD3)_2CO$): δ 10.37 (1H, br s, NH), 7.45 (1H, d, J = 7.0 Hz, ArH), 7.03-6.95 (2H, m, ArH), 3.01-2.94 (2H, m, $CH_2CH_2CO_2$), 2.50-2.42 (2H, m, $CH_2CH_2CO_2$), 2.49 (3H, s, $ArCH_3$).

Analysis calculated for $C_{24}H_{24}N_2O_4S_2$ requires:

C, 61.5; H, 5.2; N, 6.0%.

Found: C, 61.3; H, 5.1; N, 6.0%.

EXAMPLE D

Preparation of Compounds 21-23 and 70 of Table 1 by the Method Outlined in Scheme 4

Powdered Na_2CO_3 (0.70 g, 6.61 mmol) was added to a suspension of P_2S_5 (2.93 g, 6.61 mmol) in THF (40 mL) and the mixture was stirred vigorously at 20°C until homogeneous, and gas evolution had ceased (15 minutes). A solution of 1-methyl-2-indolinone [VII: R_1 = R_3 = Me] (0.80 g, 5.50 mmol) in THF (10 mL) was added and stirring was continued for 18 hours. After pouring into brine, the mixture was extracted into EtOAc, worked up, and chromatographed on silica. Elution with EtOAc/petroleum ether (1:4) gave 1-methyl-2-indolinethione [IX: R_1 = R_3 = Me] (0.71 g, 87%); mp 108-109°C (Hino T, Tsuneoka K, Nakagawa M, Akaboshi S, Chem. Pharm. Bull. 1969;17:550 record 109-111°C).

A solution of the above 1-methyl-2-indolinethione (4.1 g) in THF (150 mL) was treated dropwise over

15 minutes with an ice-cooled suspension of NaH (57%, 1.4 g) in THF (100 mL). The mixture was stirred for 30 minutes, then a solution of phenyl isocyanate (3.5 g) in THF (50 mL) was added, and stirring continued for 3 hours at 20°C. The solvent was removed under vacuum, then the residue decomposed with ice-HCl, and extracted in CH_2Cl_2. Removal of the solvent gave an oil (6.0 g), which crystallized from ether. Two recrystallizations from THF-ether gave N-phenyl (1-methyl-2-thioxo-3-indolinyl)carboxamide [IV: R_1 = H, R_2 = CONHPh, R_3 = Me] (**21**) (2.8 g, 39%) as a pale yellow solid; mp 149-151°C.

^{1}H NMR ($CDCl_3$): δ 10.36 (1H, s, NH), 7.87 (1H, d, J = 7.4 Hz, ArH), 7.60 (2H, d, J = 7.9 Hz, ArH), 7.41 (2H, t, J = 7.5 Hz, ArH), 7.31 (2H, m, ArH), 7.11 (1H, t, J = 7.3 Hz, ArH), 7.03 (1H, d, J = 7.8 Hz, ArH), 3.73 (3H, s, NCH_3).

Analysis calculated for $C_{16}H_{14}N_2OS$ requires:

C, 68.1; H, 5.1; N, 9.9; S, 11.4%.

Found: C, 67.8; H, 5.1; N, 9.8; S, 11.4%.

A solution of **21** (200 mg) in CH_2Cl_2/MeOH (2:1) (30 mL) was stirred at 20°C for 5 days, then the solvents were removed under reduced pressure. Chromatography on silica gel, eluting with CH_2Cl_2 then $CHCl_3$/EtOH (99:1), gave bis[N-phenyl 1-methylindolyl-3-carboxamide-(2)] disulfide [V: R_1 = H, R_2 = CONHPh, R_3 = Me] (**70**) (0.19 g, 95%); mp (benzene) 187-188°C.

^{1}H NMR ($CDCl_3$): δ 8.21 (1H, s, NH), 8.01 (1H, d, J = 8.1 Hz, ArH), 7.19 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.13 (4H, d, J = 4.3 Hz, Ph), 7.09 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.05 (1H, d, J = 8.1 Hz, ArH), 6.98 (1H, quin, J = 4.3 Hz, Ph), 3.77 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): δ 161.57 (CO), 138.55, 137.95 (2xs), 128.64 (d), 127.41, 126.07 (2xs), 125.55, 122.28, 122.00 (4xd), 119.76 (s), 119.27, 110.14 (2xd), 30.33 (NCH_3).

Analysis calculated for $C_{32}H_{26}N_4O_2S_2$ requires:
C, 68.3; H, 4.6; N, 10.0; S, 11.4%.
Found: C, 68.9; H, 4.9; N, 9.6; S, 11.1%.

A solution of 21 (200 mg) in Me_2CO (20 mL) was treated with K_2CO_3 (0.12 g) and methyl iodide (0.14 g) and the mixture stirred at 20°C for 1 hour. CH_2Cl_2 (100 mL) was added, then the solution filtered and the solvents removed, to yield a brown oil (0.26 g). Chromatography on silica gel, eluting with CH_2Cl_2, gave N-phenyl (1-methyl-2-methylthio-3-indolyl)carboxamide as an oil [X: R_1 = H, R_2 = CONHPh, R_3 = Me, R4 = SMe] (22) (200 mg, 95%), which crystallized from $MeOH/CH_2Cl_2$ as a white solid; mp 116-118°C.

^1H NMR ($CDCl_3$): δ 9.99 (1H, s, NH), 8.58 (1H, d, J = 8.0 Hz, ArH), 7.75 (2H, d, J = 7.6 Hz, ArH), 7.38 (4H, m, ArH), 7.29 (1H, quin, J = 4.3 Hz, ArH), 7.12 (1H, t, J = 7.4 Hz, ArH), 3.95 (3H, s, NCH_3), 2.47 (3H, s, SCH_3).

^{13}C NMR ($CDCl_3$): δ 162.59 (s, CONH), 138.80, 137.46, 131.43 (3xs, ArH), 129.03 (2xd, ArH), 127.35 (s, ArH), 124.14, 123.67, 123.02, 122.24 (4xd, ArH), 119.86 (2xd, ArH), 114.04 (s, ArH), 109.69 (d, ArH), 30.23 (q, NCH_3), 20.50 (q, SCH_3).

Analysis calculated for $C_{17}H_{16}N_2OS$ requires:
C, 68.9; H, 5.4; N, 9.5; S, 10.8%.
Found: C, 68.6; H, 5.5; N, 9.4; S, 10.8%.

Benzyl mercaptan (0.02 mL, 0.178 mmol) was added to a suspension of 70 (50 mg, 89 mmol) and BF3-etherate (1 drop) in CH_2Cl_2 (1 mL). After stirring at 20°C for 3 hours, the homogeneous mixture was poured into

saturated aqueous NaHCO3, diluted with CH_2Cl_2 and worked up, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2/petroleum ether (1:1) gave foreruns, and elution with CH_2Cl_2 elute benzyl [N-phenyl 1-methylindolyl-3-carboxamide-(2)]disulfide [XI: R_1 = H, R_2 = CONHPh, R_3 = Me, R4 = S_2CH_2Ph] (23) (39 mg, 54%); mp ($CHCl_3$/petroleum ether) 146-148°C.
^{1}H NMR: δ 8.95 (1H, br s, CONH), 8.47 (1H, dd, J = 7.7, 1.3 Hz, ArH-4), 7.66 (2H, dd, J = 7.5, 1.2 Hz, Ph), 7.40-7.07 (11H, m, ArH-5,-6,-7 and Ph), 3.90 (3H, s, NMe).
^{13}C NMR: δ 162.31 (CONHPh), 138.31 (s), 138.04 (s), 135.13 (s), 130.00 (s), 129.15, 129.06, 128.69, 127.83, 126.83 (s), 124.79, 123.94, 122.80, 122.36, 119.90, 109.92, 42.51 (CH_2Ph), 30.73 (NCH_3).
Analysis calculated for $C_{23}H_{20}N_2S_2O$ requires:
C, 68.3; H, 5.0; N, 6.9; S, 15.9%.
Found: C, 68.4; H, 5.1; N, 6.9; S, 16.0%

Compound 71 of Table 1

Similarly was prepared, from 1-ethyl-2-indolinethione (Kendall JD, Ficken GE, British Patent 829,584, Chem. Abstr. 1960;54:12847h) and phenyl isocyanate, bis[N-phenyl 1-ethylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = H, R_2 = CONHPh, R_3 = Et] (71) (25% yield); mp 200-202°C.
^{1}H NMR ($CDCl_3$): δ 8.22 (1H, br, CONH), 7.98 (1H, d, J = 8.1 Hz, H-4), 7.18 (1H, t, J = 8.0 Hz, H-6), 7.11-7.04 (6H, m, H-5 and Ph), 6.95 (1H, dd, J = 8.0, 1.0 Hz, H-7), 4.32 (2H, q, J = 7.0 Hz, NCH_2CH_3), 1.36 (3H, t, J = 7.0 Hz, NCH_2CH_3).
^{13}C NMR: δ 161.73 (CONH), 137.91 (s), 137.44 (s), 128.55, 128.55, 128.35 (2s), 126.33 (s), 125.41,

123.47, 122.12, 122.07, 119.37, 110.19 (C-7), 38.86 ($N\underline{C}H_2CH_3$), 15.23 ($NCH_2\underline{C}H_3$).

Analysis calculated for $C_{34}H_{30}N_4S_2O_2$ requires:
C, 69.1; H, 5.1; N, 9.5; S, 10.8%.
Found: C, 68.9; H, 5.4; N, 9.5; S, 10.4%.

Compound 72 of Table 1

Similarly was prepared 4-chloro-1-methyl-2-indolinethione [IX: R_1 = 4-Cl, R_3 = Me] (92% yield); mp 147.5-149.5°C.

^1H NMR ($CDCl_3$): δ 7.29 (1H, t, J = 8.0 Hz, H-6), 7.13 (1H, d, J = 8.0 Hz, H-5), 6.86 (1H, d, J = 8.0 Hz, H-7), 4.09 (2H, s, H-3), 3.60 (3H, s, NCH_3).

^{13}C NMR: δ 200.75 (C-2), 147.65 (s), 130.04 (s), 129.52, 127.44 (s), 124.34, 107.81 (C-7), 48.42 (C-3), 31.55 (NCH_3).

Analysis calculated for C_9H_8ClNS requires:
C, 54.7; H, 4.1; N, 7.1; S, 16.2%.
Found: C, 54.5; H, 4.3; N, 7.1; S, 16.0%.

Reaction of this with phenyl isocyanate as above gave bis[N-phenyl 4-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 4-Cl, R_2 = CONHPh, R_3 = Me] (72) (21% yield); mp 225-228°C.

^1H NMR ($CDCl_3$): δ 8.38 (1H, br, NH), 7.49 (1H, dd, J = 7.9, 1.5 Hz, H-5), 7.12 (1H, t, J = 7.9 Hz, H-6), 7.08-7.05 (4H, m, CONH<u>Ph</u>), 6.98 (1H, dd, J = 7.9, 1.5 Hz, H-7), 6.96 (1H, m, CONH<u>Ph</u>), 3.77 (3H, S, $N-CH_3$).

Analysis calculated for $C_{32}H_{24}Cl_2N_4O_2S_2$ requires:
C, 60.8; H, 3.8; N, 8.9; Cl, 11.2%.
Found: C, 60.7; H, 4.1; N, 8.7; Cl, 11.8%.

Compound 73 of Table 1

Similarly was prepared, from 5-chloro-1-methyl-2-indolinethione [IX: R_1 = 5-Cl, R_3 = Me]; mp 163-165°C (Baudin J-B, Julia SA, Lorne R, Bull. Soc. Chim. Fr. 1987:181-188 records mp 153-155°C) and phenyl isocyanate, bis[N-phenyl 5-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 5-Cl, R_2 = CONHPh, R_3 = Me] (73) (27% yield); mp 214-216°C.

^{1}H NMR ($CDCl_3$): δ 8.14 (1H, br, CONH), 7.94 (1H, d, J = 1.8 Hz, H-4), 7.12 (4H, br, ArH), 7.07 (1H, d, J = 8.4 Hz, ArH), 7.01 (1H, m, ArH), 6.90 (1H, d, J = 8.9 Hz, ArH), 3.76 (3H, s, NCH_3).

^{13}C NMR: δ 161.06 (CONH), 137.72 (s), 136.81 (s), 128.73, 128.44 (s), 128.25 (s), 126.58 (s), 126.11, 123.76, 121.27, 119.71 (s), 118.80, 111.16 (C-7), 30.53 (NCH_3).

Analysis calculated for $C_{32}H_{24}Cl_2N_4O_2S_2$ requires:

C, 60.8; H, 3.8; N, 8.9; S, 10.2%.

Found: C, 60.6; H, 4.0; N, 8.9; S, 10.2%.

$NaBH_4$ (14 mg, 0.38 mmol) was added to a stirred suspension of the above compound (0.12 g, 0.19 mmol) in MeOH (5 mL). After 15 minutes, the solution was concentrated to dryness and the residue was partitioned between EtOAc and water. The organic solution was worked up to give a solid which was recrystallized from degassed $CHCl_3$/benzene at -5°C to give *N*-phenyl 5-chloro-1-methyl-2-thioxoindole-3-carboxamide (20) [IV: R_1 = 5-Cl, R_2 = CONHPh, R_3 = Me] as coarse needles (86% yield); mp 312-320°C (dec).

^{1}H NMR ($(CD_3)_2SO$): δ 12.84 (1H, s, SH), 8.09 (1H, d, *J* = 2.2 Hz, H-4), 7.70 (2H, d, *J* = 8.5 Hz, H-2',6'), 7.27 (2H, dd, J = 8.5, 8.2 Hz, H-3',5'), 7.07 (1H, d, *J* = 8.4 Hz, H-7), 6.92 (1H, t, *J* = 8.2 Hz, H-4'), 6.86 (1H, dd, *J* = 8.4, 2.2 Hz, H-6), 3.64 (3H, s, N-CH_3).

^{13}C NMR: δ 164.73 (CONH), 140.81 (s), 135.17 (s), 130.29 (s), 128.55 (d), 123.93 (s), 121.01 (d), 118.20 (d), 117.65 (d), 117.30 (d), 107.97 (d), 104.40 (s), 29.18 ($N\text{-}CH_3$).

Analysis calculated for $C_{16}H_{13}ClN_2OS$ requires:
M+ 318.0408, 316.0437.
Found: M+ (mass spectrum) 318.0414, 316.0431.

Compound 74 of Table 1

Similarly was prepared, from 7-chloro-1-methyl-2-indolinethione [IX: R_1 = 7-Cl, R_3 = Me]; mp 126-128°C (Inoue S, Uematsu T, Kato T, Ueda K, Pestic. Sci. 1985;16:589-598 records mp 125-127°C) and phenyl isocyanate, bis[N-phenyl-7-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 7-Cl, R_2 = CONHPh, R_3 = Me] (74) (27% yield); mp 232-234°C.

^1H NMR ($CDCl_3$): δ 8.15 (1H, br, CONH), 7.85 (1H, d, J = 8.0 Hz, H-4), 7.19-7.05 (5H, m, ArH), 7.00 (1H, t, J = 6.6 Hz, ArH), 6.90 (1H, t, J = 7.8 Hz, ArH), 4.25 (3H, s, $N\text{-}CH_3$).

Analysis calculated for $C_{32}H_{24}Cl_2N_4O_2S_2$ requires:
C, 60.8; H, 3.8; N, 8.9%.
Found: C, 60.4; H, 4.0; N, 8.8%.

Compound 75 of Table 1

1,4-Dimethyl-2-indolinethione [IX: R_1 = 4-Me, R_3 = Me] (81%); mp 160-162°C.

Analysis calculated for $C_{10}H_{11}NS$ requires:
C, 67.8; H, 6.3; N, 7.9; S, 18.1%
Found: C, 68.0; H, 6.4; N, 8.0; S, 18.3%
was prepared by the method given for Compound 77 (below).

Reaction of this with phenyl isocyanate gave bis[N-phenyl 1,4-dimethylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 4-CH_3, R_2 = CONHPh, R_3 = Me] (75); mp 237-239°C.

^{1}H NMR ($CDCl_3$): δ 8.30 (1H, br s, CONH), 7.14 (1H, dd, J = 7.3, 7.3 hz, H-6), 7.04-6.86 (7H, m, H-5,7 and CONH<u>Ph</u>), 3.69 (3H, s, NCH_3), 2,47 (3H, s, 4-CH_3).

^{13}C NMR ($CDCl_3$): δ 164.57 (<u>C</u>ONHPh), 138.59, 137.62, 131.51 (3xs), 128.62 (d), 127.23 (s), 125.11 (d), 124.15 (s), 123.94, 122.62 (2xd), 122.10 (s), 119.61, 107.91 (2xs), 30.26 (NCH_3), 19.66 (4-CH_3).

Analysis calculated for $C_{34}H_{30}N_4O_2S_2$ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 69.1; H, 5.1; N, 9.7; S, 11.0%.

<u>Compound 76 of Table 1</u>

1,5-Dimethyl-2-indolinethione [IX: R_1 = 5-Me, R_3 = Me]; mp 143-145°C (<u>Bull. Fr.</u> 1987:181 reports mp 132-133°C) was prepared by the method given for Compound 77 (below). Reaction of this with phenyl isocyanate gave bis[N-phenyl 1,5-dimethylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 5-CH_3, R_2 = CONHPh, R_3 = Me] (76); mp 231-234°C.

^{1}H NMR ($CDCl_3$): δ 8.24 (1H, br s, CONH), 7.78 (1H, br, H-4), 7.19-7.13 (4H, m, CONH<u>Ph</u>), 7.05-6.90 (3H, m, H-6,7 and CONH<u>Ph</u>), 3.71 (3H, s, NCH_3), 2.36 (3H, s, 5-CH_3).

^{13}C NMR ($CDCl_3$): δ 161.75 (CONH), 138.00, 137.10, 131.77, 129.01 (4xs), 128.53, 127.37 (2xd), 126.35 (s), 123.40, 121.33, 119.85, 109.85 (4xd), 30.32 (NCH_3), 21.57 (5-CH_3).

Analysis calculated for $C_{34}H_{30}N_4O_2S_2$ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 69.4; H, 5.2; N, 9.6; S, 11.2%.

Compound 77 of Table 1

A mixture of 2,5-dimethylaniline (27.4 g, 0.2 mol) and benzotriazole (23.8 g, 0.2 mol) in EtOH (300 mL) was stirred at 20°C as 37% aqueous formaldehyde (16.1 g, 0.2 mol) was added gradually. After 30 minutes, the white solid which precipitated was collected and washed with EtOH to give N-(1-benzotriazolylmethyl)-2,5-dimethylaniline (33.9 g, 67% yield); mp (EtOH) 147-149°C.
^1H NMR ($CDCl_3$): δ 6.85-8.10 (7H, m, ArH), 6.56 (minor isomer) and 6.13 (major isomer) (2H, 2xm, CH_2), 5.08 (minor) and 4.70 (major) (1H, 2xm, NH), 2.24 (3H, s, CH_3), and 2.12 (3H, s, CH_3).
Analysis calculated for $C_{15}H_{16}N_4$ requires:
C, 70.6; H, 5.9; N, 23.5%.
Found: C, 71.5; H, 6.3; N, 22.1%.

A suspension of this compound (33 g, 0.13 mol) and $NaBH_4$ (5 g) in dioxane (400 mL) was heated under reflux for 5 hours, and the solution was concentrated. After cooling, water was added and the resulting mixture was extracted with EtOAc. The organic layer was washed twice with aqueous K_2CO_3 and water, and dried (Na_2SO_4). Removal of the solvent gave N,2,5-trimethylaniline (17.6 g, 99% yield) as an oil, which was used directly.
^1H NMR ($CDCl_3$): δ 6.93 (1H, d, J = 7.4 Hz, H-3), 6.49 (1H, d, J = 7.6 Hz, H-4), 6.44 (1H, s, H-6), 3.72, (1H, s, NH), 2.88 (3H, s, NCH_3), 2.31 (3H, s, CH_3), and 2.09 (3H, s, CH_3).

A solution of 2,4,6-trimethylaniline (6.86 g, 5 mmol) in dry THF (100 mL) under an atmosphere of N_2 was cooled to -78°C and n-butyllithium (21 mL, 2.5 M solution in hexanes) was added dropwise. The mixture was allowed to warm to 0°C, and dry CO_2 gas was bubbled in for 2-3 minutes. The excess CO_2 was removed under

vacuum, and after the addition of further THF to replace that lost by evaporation, the solution was recooled to -78°C. n-Butyllithium (22 mL, 2.5 M solution in hexanes) was again added dropwise, and the temperature was then allowed to rise slowly to -10°C where a deep red colored solution was obtained. After a further 30 minutes at that temperature, the mixture was again recooled to -78°C and CO_2 gas was bubbled in until the red color disappeared. The reaction mixture was allowed to warm to 20°C, and after removal of the solvent, 0.1 M HCL (50 mL) was added to initiate both deprotection of the nitrogen and ring-closure. The resulting mixture was extracted with EtOAc, and this was then washed successively with 0.1 M HCl, water, and dilute aqueous Na_2CO_3. After drying (Na_2SO_4), the solvent was removed under vacuum, to leave an oil which was purified by chromatography on Al_2O_3 to give 1,6-dimethyl-2-indolinone (3.37 g, 42% yield) [VII: R_1 = 6-Me; R_3 = Me]; mp (hexane) 94.5-96°C. ^{1}H NMR ($CDCl_3$): δ 7.11 (2H, d, J = 7.5 Hz, H-4), 6.85 (2H, d, J = 7.5 Hz, H-5), 6.65 (1H, s, H-7), 3.47 (2H, s, CH_2), 3.19 (3H, s, 1-CH_3), and 2.38 (3H, s, 6-CH_3).

Analysis calculated for $C_{10}H_{11}NO$ requires:
C, 74.5; H, 6.9; N, 8.7%.
Found: C, 74.5; H, 6.6; N, 8.7%.

Thiation of this with P_2S_5 as above gave 1,6-dimethyl-2-indolinethione [IX: R_1 = 6-Me, R_3 = Me]; mp 141-143°C.

Analysis calculated for $C_{10}H_{11}NS$ requires:
C, 67.8; H, 6.3; N, 7.9; S, 18.1%.
Found: C, 67.6; H, 6.5; N, 8.2; S, 18.0%.

This was reacted with phenyl isocyanate as above to give bis[N-phenyl 1,6-dimethylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 6-CH_3, R_2 = CONHPh, R_3 = Me] (77); mp 192-195°C.

^{1}H NMR ($CDCl_3$): δ 8.16 (1H, br s, CONH), 7.85 (1H, d, J = 8.3 Hz, H-4), 7.10 (4H, br, CONHPh, 6.98 (1H, m, CONHPh), 6.87 (1H, d, J = 8.3 Hz, H-5), 6.73 (1H, br, H-7), 3.71 (3H, s, NCH_3), 2.35 (3H, s, 6-CH_3).

^{13}C NMR ($CDCl_3$): δ 161.49 (CONH), 139.05, 137.98, 135.63 (3xs), 128.44 (d), 126.10 (s), 124.28 (d), 124.06 (s), 123.17, 121.61, 119.21, 109.85 (4xd), 30.17 (NCH_3), 21.98 (6-CH_3).

Analysis calculated for $C_{34}H_{30}N_4O_2S_2$ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 68.9; H, 5.2; N, 9.6; S, 11.0%.

Compound 78 of Table 1

Similarly was prepared 1,7-dimethyl-2-indolinethione [IX: R_1 = 7-Me, R_3 = Me]; mp 138-9°C.

Analysis calculated for $C_{10}H_{11}NS$ requires:

C, 67.8; H. 6.3; N, 7.9; S, 18.1%.

Found: C, 67.6; H, 6.2; N, 8.0; S, 18.1%.

Reaction of this with phenyl isocyanate gave bis[N-phenyl 1,7-dimethylindolyl-3-carboxamide-(2)]-disulfide [V: R_1 = 7-CH_3, R_2 = CONHPh, R_3 = Me] (78); mp 221-223°C.

^{1}H NMR ($CDCl_3$): δ 8.11 (1H, br s, CONH), 7.83 (1H, J = 8.1 Hz, H-4), 7.15-7.07 (4H, m, CONHPh), 6.99 (1H, m, CONHPh), 6.94 (1H, dd, J = 8.1, 8.1 Hz, H-5), 6.85 (1H, d, J = 8.1 Hz, H-6), 4.07 (3H, s, NCH_3), 2.44 (3H, s, 7-CH_3).

^{13}C NMR ($CDCl_3$): δ 161.67 (CONH), 137.95, 137.86 (2xs), 128.55, 128.31 (2xd), 126.85 (s), 123.57, 122.10

(2xd), 121.77 (s), 119.72, 119.21 (2xd), 33.36 (NCH_3), 20.23 (7-CH_3).

Analysis calculated for $C_{34}H_{30}N_4O_2S_2$ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 69.1; H, 5.2; N, 9.7; S, 11.0%.

<u>Compound 79 of Table 1</u>

Similarly was prepared, from 4-methoxy-1-methyl-2-indolinethione [IX: R_1 = 4-OMe, R_3 = Me]; mp 141-144°C (US Patent 5,030,646 records mp 126-128°C) and phenyl isocyanate, bis[N-phenyl 4-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 4-OCH_3, R_2 = CONHPh, R_3 = Me] (79); mp 225-228°C.

^{1}H NMR ($CDCl_3$): δ 8.85 (1H, br s, CONH), 7.25-7.06 (5H, m, H-6 and CONH<u>Ph</u>), 6.98 (1H, m, CONH<u>Ph</u>), 6.82 (1H, d, J = 8.3 Hz, H-7), 6.36 (1H, d, J = 7.8 Hz, H-5), 3.76 (3H, s, OCH_3), 3.69 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): 162.36 (CONH), 152.70, 139.39, 138.73, 130.20 (4xs), 128.54, 125.39, 123.08 (3xs), 130.20 (s), 128.54, 125.39, 123.08 (3xd), 19.96 (s), 119.19 (d), 114.66 (s), 103.67, 101.55 (2xd), 22.58 (OCH_3), 30.48 (NCH_3).

Analysis calculated for $C_{34}H_{30}N_4O_4S_2$ requires:

C, 65.6; H, 4.9; N, 9.0; S, 10.3%.

Found: C, 65.7; H, 4.9; N, 9.2; S, 10.2%.

<u>Compound 80 of Table 1</u>

Similarly was prepared, from 5-methoxy-1-methyl-2-indolinethione [IX: R_1 = 5-OMe, R_3 = Me]; mp 148-150°C (US Patent 5,030,646 records mp 142-144°C) and phenyl isocyanate, bis[N-phenyl 5-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide

[V: R_1 = 5-OCH_3, R_2 = CONHPh, R_3 = Me] (80); mp 161-164°C.

^{1}H NMR ($CDCl_3$): δ 8.41 (1H, br s, CONH), 7.55 (d, J = 1.8 Hz, H-4), 7.18 (4H, m, CONHPh), 7.00 (2H, m, H-6 and CONHPh), 6.89 (1H, d, J = 7.4 Hz, H-7), 3.82 (3H, s, OCH_3), 3.68 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): δ 161.80 (CONH), 155.94, 137.87, 134.07 (3xs), 128.71, 123.68, 119.50, 117.48, 111.10, 102.29 (6xd), 55.63 (OCH_3), 30.47 (NCH_3).

Analysis calculated for $C_{34}H_{30}N_4O_4S_2$ requires:
C, 65.6; H, 4.9; N, 9.0; S, 10.3%.
Found: C, 65.3; H, 5.1; N, 9.2; S, 10.4%.

Compound 81 of Table 1

Similarly was prepared, from 6-methoxy-1-methyl-2-indolinethione [IX: R_1 = 6-OMe, R_3 = Me]; mp 133-136°C (US Patent 5,030,646 records mp 135-136°C) and phenyl isocyanate, bis[N-phenyl 6-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 6-OCH_3, R_2 = CONHPh, R_3 = Me] (81); mp 197-200°C.

^{1}H NMR ($CDCl_3$): δ 8.19 (1H, br s, CONH), 7.91 (1H, d, J = 8.9 Hz, H-4), 7.12 (4H, br, CONHPh), 6.97 (1H, m, CONHPh), 6.71 (1H, d, J = 8.9 Hz, H-5), 6.25 (1H, br, H-7), 3.74 (3H, s, OCH_3), 3.70 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): δ 161.37 (CONH), 158.75, 139.82, 138.04, 128.65 (4xs), 128.50, 123.30, 123.12, (3xd), 120.64, 120.26 (2xs), 119.10, 113.22, 98.02 (3xd), 55.26 (OCH_3), 30.21 (NCH_3).

Analysis calculated for $C_{34}H_{30}N_4O_4S_2$ requires:
C, 65.6; H, 4.9; N, 9.0; S, 10.3%.
Found: C, 65.5; H, 4.8; N, 9.2; S, 10.4%.

Compound 82 of Table 1

Similarly was prepared, from 7-methoxy-1-methyl-2-indolinethione [IX: R_1 = 7-OMe, R_3 = Me]; mp 124-126°C (US Patent 5,030,646 records mp 114-116°C) and phenyl isocyanate, bis[N-phenyl 7-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = 7-OCH_3, R_2 = CONHPh, R_3 = Me] (82); mp 205-208°C.

^{1}H NMR ($CDCl_3$): δ 8.14 (1H, br s, CONH), 7.57 (1H, d, J = 8.2 Hz, H-4), 7.13 (4H, m, CONHPh), 6.96 (1H, m, CPNHPh), 6.93 (1H, dd, J = 8.2, 8.2 Hz, H-5), 6.48 (1H, d, J = 8.2 Hz, H-6), 4.12 (3H, s, OCH_3), 3.73 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): δ 161.72 (CONH), 147.12, 137.99, 129.08 (3xs), 128.45 (d), 128.01 (s), 123.27, 122.35, 119.33, 114.13, 105.35 (5xd), 55.22 (OCH_3), 33.73 (NCH_3).

Analysis calculated for $C_{34}H_{30}N_4O_4S_2$ requires:
C, 65.6; H, 4.9; N, 9.0; S, 10.3%.
Found: C, 64.9; H, 5.0; N, 9.0; S, 10.4%.

Compound 84 of Table 1

A solution of 3-(methylthio)-5-(trifluoromethyl)-oxindole (Gassman PG, Cue BW, Luh T-Y, J. Org. Chem. 1977;42:1344-1348) (10 g, 40 mmol) in AcOH (100 mL) was heated under reflux with Zn dust (13.3 g, 0.2 mol) for 1 hour. The mixture was cooled and filtered, and the precipitate was washed with AcOH. The combined filtrates were evaporated under reduced pressure, and the residue was diluted with 1 M aqueous ammonia to give 5-trifluoromethyloxindole [VII: R_1 = 5-CF_3, R_3 = H] (7.22 g, 90%); mp (aqueous EtOH) 188.5-191°C (lit. [Hardtmann GE, USP 4,160,032; Chem. Abstr. 1979;91:P107890w]; mp 188-189°C).

^{1}H NMR ($CDCl_3$): δ 8.74 (1H, s, NH), 7.52 (1H, d, J = 8.2 Hz, H-6), 7.49 (1H, s, H-4), 6,97 (1H, d, J = 8.2 Hz, H-7), 3.61 (2H, s, CH_2).

A suspension of the above oxindole (5.03 g, 25 mmol) in water (100 mL) containing NaOH (1.5 g) was treated with Me_2SO_4 (4.7 g, 37 mmol). The mixture was warmed to 100°C for 10 minutes, cooled, a further portion of Me_2SO_4 and NaOH added, and warmed again briefly. After thorough cooling, the solid was collected and chromatographed on alumina. Elution with CH_2Cl_2/hexane (7:3) gave 1-methyl-5-(trifluoromethyl)-oxindole [VII: R_1 = 5-CF_3, R_3 = Me] (3.5 g, 65%); mp (hexane) 127.5-129°C.

^{1}H NMR ($CDCl_3$): δ 7.58 (1H, d, J = 8.2 Hz, H-6), 7.50 (1H, s, H-4), 6.89 (1H, d, J = 8.2 Hz, H-7), 3.58 (2H, s, CH_2), 3.25 (3H, s, CH_3).

Analysis calculated for $C_{10}H_8F_3NO$ requires:

C, 55.8; H, 3.8; N. 6.5%.

Found: C, 55.5; H, 3.8; N, 6.5%.

Reaction of this compound with P_2S_5 as above gave 1-methyl-5-(trifluoromethyl)-2-indolinethione [IX: R_1 = 5-CF_3, R_3 = Me] (96% yield); mp 124.5-126°C.

^{1}H NMR ($CDCl_3$): δ 7.63 (1H, dd, J = 8.3, 0.8 Hz, H-6), 7.54 (1H, d, J = 0.8 Hz, H-4), 7.03 (1H, d, J = 8.3 Hz, H-7), 4.15 (2H, s, C-3), 3.64 (3H, s, N-CH_3).

^{13}C NMR: δ 202.28 (C-2), 149.34 (s), 129.60 (s), 126.54 (J = 32.5 Hz, C-5), 125.9 (J = 4.0 Hz), 124.21 (J = 271.9 Hz) (CF_3), 121.00 (J = 3.8 Hz), 109.28 (d), 48.75 (C-3), 31.35 (N-CH_3).

Analysis calculated for ($C_{10}H_8F_3NS$) requires:

C, 51.9; H, 3.5; N, 6.3; S, 14.1%.

Found: C, 52.0; H, 3.7; N, 6.3; S, 14.1%.

Reaction of this with phenyl isocyanate as above gave 2,2-dithiobis[*N*-phenyl-1-methyl-5-(trifluoro-

methyl)indolyl-3-carboxamide] (84) [V: R_1 = 5-CF_3, R_2 = CONHPh, R_3 = Me] (71% yield); mp 214-216°C.
^{1}H NMR (($(CD_3)_2SO$): δ 9.53 (1H, s, CONH), 8.14 (1H, br s, H-4), 7.59 (1H, d, *J* = 8.8 Hz, H-7), 7.53 (1H, dd, *J* = 8.8, 1.5 Hz, H-6), 7.12-7.09 (4H, m, ArH), 6.97 (1H, m, ArH), 3.76 (3H, s, N-CH_3).
^{13}C NMR: δ 160.49 (CONH), 138.93 (s), 138.21 (s), 131.76 (s), 128.19 (d), 124.96 (*J* = 271.6 Hz, CF_3), 124.60 (d), 119.21 (s), 119.09 (d), 118.57 (*J* = 4.1 Hz), 30.46 (N-CH_3).
Analysis calculated for $C_{34}H_{24}F_6N_4O_2S_2$ requires:
C, 58.4; H, 3.5; N, 8.0; S, 9.2%.
Found: C, 58.5; H, 3.8; N, 7.9; S, 9.3%.

Compound 85 of Table 1

Methylation of 6-chlorooxindole [VII: R_1 = 6-Cl, R_3 = H] (Quallich GJ, Morrissey PM, Synthesis 1993:51-53) with Me_2SO_4/NaOH as above gave 6-chloro-1-methyloxindole [VII: R_1 = 6-Cl, R_3 = CH_3]; mp (aqueous EtOH) 119.5-122°C.
^{1}H NMR ($CDCl_3$): δ 7.15 (1H, d, *J* = 7.8 Hz, H-4), 7.01 (1H, dd, *J* = 7.8, 1.8 Hz, H-5), 6.82 (1H, d, *J* = 1.7 Hz, H-7), 3.49 (2H, s, CH_2), 3.19 (3H, s, CH_3).
Analysis calculated for C_9H_8ClNO requires:
C, 59.5; H, 4.4; N, 7.7%.
Found: C, 59.6; H, 4.6; N, 7.6%.

Reaction of this with P_2S_5 as above gave 6-chloro-1-methyl-2-indolinethione [IX: R_1 = 6-Cl, R_3 = Me] (87% yield); mp (EtOAc/petroleum ether) 162-165°C.
^{1}H NMR ($CDCl_3$): δ 7.20 (1H, d, *J* = 7.9 Hz, H-4), 7.13 (1H, dd, *J* = 7.9, 1.7 Hz, H-5), 6.96 (1H, d, *J* = 1.7 Hz, H-7), 4.06 (2H, s, H-3), 3.59 (3H, s, N-CH_3).

^{13}C NMR: δ 202.00 (C-2), 147.76 (s), 133.98 (s), 127.35 (s), 124.64 (d), 124.06 (d), 110.20 (d), 48.59 (C-3), 31.29 ($N-CH_3$).

Analysis calculated for $C_9H_8ClN_2SO$ requires:

C, 54.7; H, 4.1; N, 7.1; S, 16.2%.

Found: C, 54.8; H, 4.1; N, 7.0; S, 16.3%.

Reaction of this with phenyl isocyanate as above gave bis[N-phenyl 6-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide (85) [V: R_1 = 6-Cl, R_2 = CONHPh, R_3 = Me] (61% yield); mp 243-245°C.

^1H NMR ($(CD_3)_2SO$): δ 9.43 (1H, br, CONH), 7.77 (1H, d, J = 8.6 Hz, H-4), 7.46 (1H, d, J = 1.4 Hz, H-7), 7.19-7.09 (5H, m, ArH), 7.01 (1H, m, ArH), 3.67 (3H, s, $N-CH_3$).

^{13}C NMR: δ 160.66 (CONH), 138.29 (s), 138.04 (s), 129.87 (s), 129.41 (s), 128.15 (d), 123.94 (s), 122.91 (d), 122.37 (d), 121.70 (d), 119.20 (s), 119.12 (d), 110.69 (d), 30.22 ($N-CH_3$).

Analysis calculated for $C_{32}H_{24}Cl_2N_4O_2S_2$ requires:

C, 60.9; H, 3.8; N, 8.9; S, 10.2%.

Found: C, 60.9; H, 4.0; N, 8.7; S, 10.2%.

Compound 86 of Table 1

Similarly was prepared, from 1-methyl-5-nitro-2-oxindole (Robinson R, Wyler M, J. Chem. Soc. 1941:620-624), 1-methyl-5-nitro-2-indolinethione [IX: R_1 = 5-NO_2, R_3 = Me] (68% yield); mp (EtOAc/light petroleum) >330°C.

^1H NMR ($(CD_3)_2SO$): δ 8.28 (1H, dd, J = 8.7, 1.7 Hz, H-6), 8.17 (1H, d, J = 1.7 Hz, H-4), 7.41 (1H, d, J = 8.7 Hz, H-7), 4.26 (2H, s, H-3), 3.60 (3H, s, $N-CH_3$).

^{13}C NMR: δ 203.48 (C-2), 151.49 (s), 143.81 (s), 130.53 (s), 124.80 (d), 119.00 (d), 110.24 (d), 48.45 (C-3), 31.34 ($N-CH_3$).

Analysis calculated for $C_9H_8N_2SO_2$ requires:

M+ 208.0306.

Found: M+ 208.0311 (mass spectrum).

Reaction of this with phenyl isocyanate as above gave 2,2'-dithiobis[*N*-phenyl-1-methyl-5-nitroindolyl-3-carboxamide] (86) [V: R_1 = 5-NO_2, R_2 = CONHPh, R_3 = Me] (52% yield); mp 236-240°C (dec).

^1H NMR ($(CD_3)_2CO$): δ 9.68 (1H, br, CONH), 8.64 (1H, d, *J* = 1.6 Hz, H, H-4), 8.07 (1H, dd, *J* = 8.8, 1.6 Hz, H-6), 7.56 (1H, d, *J* = 8.8 Hz, H-7), 7.18-7.08 (4H, m, ArH), 6.98 (1H, t, *J* = 6.8 Hz, ArH), 3.79 (3H, s, $N-CH_3$).

^{13}C NMR: δ 160.04 (CONH) 141.96 (s), 140.17 (s), 138.22 (s), 128.24 (d), 124.35 (s), 123.09 (d), 120.25 (s), 118.90 (d), 117.76 (d), 111.64 (d), 30.70 ($N-CH_3$).

Analysis calculated for $C_{32}H_{24}N_6O_6S_2 \cdot 0.2H_2O$ requires:

C, 55.8; H, 4.1; N, 12.2%.

Found: C, 55.5; H, 3.9; N, 12.0%.

Analysis calculated for $C_{32}H_{25}N_6S_2O_6$ requires:

$[M + H]^+$ 653.1277.

Found: $[M + H]^+$ 653.1275 (FAB mass spectrum).

Compound 87 of Table 1

Similarly was prepared, from 5-fluoro-1-methyloxindole (Wiseman EH, Chiaini J, McManus JM, J. Med. Chem. 1973;16:131-134), 5-fluoro-1-methyl-2-indolinethione [IX: R_1 = 5-F, R_3 = Me] (93% yield); mp 155-157°C.

^1H NMR ($CDCl_3$): δ 7.11-6.99 (2H, m, H-4,6), 6.88 (1H, dd, *J* = 9.3, 4.2 Hz, H-7), 4.09 (2H, s, H-3), 3.61 (3H, s, $N-CH_3$).

^{13}C NMR: δ 200.61 (C-2), 160.49 (J = 243.6 Hz, C-5), 142.76 (s), 130.80 (J = 8.6 Hz, C-3a), 114.48 (J = 24.1 Hz), 112.13 (J = 25.1 Hz), 109.94 (J = 8.6 Hz), 48.96 (J = 1.8 Hz, C-3), 31.38 ($N-CH_3$).
Analysis calculated for C_9H_8FNS requires:
C, 59.7; H, 4,5; N, 7.7; S, 17.7%.
Found: C, 59.7; H, 4.6; N, 7.8; S, 17.4%.

Reaction of this with phenyl isocyanate as above gave 2,2'-dithiobis[*N*-phenyl-5-fluoro-1-methylindolyl-3-carboxamide] (87) [V: R_1 = 5-F, R_2 = CONHPh, R_3 = Me]) (74% yield); mp 205-207°C.
^1H NMR ($CDCl_3$): δ 8.17 (1H, br, CONH), 7.64 (1H, dd, J = 9.4, 2.0 Hz, H-4), 7.17 (4H, br d, ArH), 7.00 (1H, m, ArH), 6.95-6.88 (2H, m, ArH), 3.78 (3H, s, $N-CH_3$).
^{13}C NMR: δ 161.17 (CONH), 158.97 (J = 239.4 Hz, C-5), 138.02 (s), 135.71 (s), 128.69 (d), 123.69 (d), 118.87 (d), 114.66 (J = 27.1 Hz), 111.14 (J = 10.0 Hz), 106.92 (J = 25.5 Hz), 30.61 ($N-CH_3$).
Analysis calculated for $C_{32}H_{24}F_2N_4O_2S_2$ requires:
C, 64.2; H, 4.0; N, 9.4; S, 10.7%.
Found: C, 63.9; H, 4.2; N, 9.3; S, 10.7%.

Compound 88 of Table 1

Reduction of 5-cyano-3-methylthiooxindole (Gassman PG, Cue BW, Luh T-Y, *J. Org. Chem.* 1977;42:1344-1348) with Zn/AcOH as above gave 5-cyanooxindole [VII: R_1 = 5-CN; R_3 = H] (89% yield); mp (aqueous EtOH) 249°C (dec) (lit. [Gassman PG, Gilbert DP, Luh T-Y, JOC 1977;42:1340-1344]; mp 249-251°C). Methylation of this with Me_2SO_4/NaOH as above gave 5-cyano-1-methyloxindole [VII: R_1 = 5-CN, R_3 = H] (53% yield); mp (hexane) 201-203°C.

^1H NMR ($CDCl_3$): δ 7.63 (1H, dd, J = 8.1, 1.1 Hz, H-6), 7.51 (1H, d, J = 1.1 Hz, H-4), 6.90 (1H, d, J = 8.1 Hz, H-7), 3.57 (2H, s, CH_2), 3.25 (3H, s, CH_3).
Analysis calculated for $C_{10}H_8N_2O$ requires:
C, 69.8; H, 4.7; N, 16.3%.
Found: C, 70.2; H, 4.64; N, 16.7%.

Reaction of the above compound with P_2S_5 gave 5-cyano-1-methyl-2-indolinethione [IX: R_1 = 5-CN, R_3 = Me] (41% yield); mp 185-187°C.
^1H NMR ($(CD_3)_2SO$): δ 7.87 (1H, br d, J = 8.3 Hz, H-6), 7.76 (1H, br s, H-4), 7.41 (1H, d, J = 8.3 Hz, H-7), 4.22 (2H, s, H-3), 3.58 (3H, s, N-CH_3).
^{13}C NMR: δ 202.34 (C-2), 149.78 (s), 133.05 (d), 130.42 (s), 126.92 (d), 119.05 (s), 110.98 (d), 48.20 (C-3), 31.11 (N-CH_3).
Analysis calculated for $C_{10}H_8N_2S \cdot 0.5H_2O$ requires:
C, 60.7; H, 4.6; N, 14.2%.
Found: C, 61.3; H, 4.1; N, 14.4%.

Reaction of this with phenyl isocyanate as above gave 2,2'-dithiobis[*N*-phenyl-5-cyano-1-methylindolyl-3-carboxamide] (88) [V: R_1 = 5-CN, R_2 = CONHPh, R_3 = Me] (47% yield); mp 221-224°C.
^1H NMR ($(CD_3)_2SO$): δ 9.51 (1H, s, CONH), 8.18 (1H, br s, H-4), 7.60-7.48 (2H, m, H-6,7), 7.20-7.06 (4H, m, ArH), 7.00 (1H, br s, ArH), 3.75 (3H, s, N-CH_3).
^{13}C NMR: δ 160.21 (CONH), 138.97 (s), 138.26 (s), 132.74 (C-5), 128.77 (s), 128.27 (d), 126.52 (d), 124.72 (s), 123.14 (d), 119.80 (s), 119.11 (d), 118.87 (s), 112.29 (d), 103.53 (CN), 30.46 (N-CH_3).
Analysis calculated for $C_{34}H_{24}N_6O_2S_2 \cdot 0.5H_2O$ requires:
C, 65.7; H, 4.1; N, 13.5; S, 10.3%.
Found: C, 65.6; H, 4.0; N, 13.5; S, 10.6%.

Compound 89 of Table 1

Similarly was prepared, from 5-bromo-1-methyl-2-indolinethione [IX: R_1 = 5-Br, R_3 = Me]; mp 137-139°C, (Baudin J-B, Julia SA, Lorne R, Bull. Soc. Chim. France 1987:181 records mp 126-127°C) and phenyl isocyanate as above, 2,2'-dithiobis[*N*-phenyl-5-bromo-1-methylindolyl-3-carboxamide] (**89**) [V: R_1 = 5-Br, R_2 = CONHPh, R_3 = Me] (68% yield); mp 219-221°C.

^{1}H NMR ($CDCl_3$): δ 8.14 (1H, br, CONH), 8.10 (1H, d, *J* = 1.6 Hz, H-4), 7.21-7.12 (5H, m, ArH), 7.01 (1H, m, ArH), 6.83 (1H, br d, *J* = 8.2 Hz, ArH), 3.73 (3H, s, N-CH_3).

^{13}C NMR: δ 161.04 (CONH), 137.68 (s), 137.00 (s), 128.75 (d), 128.60 (d) 127.13 (s), 124.29 (d), 123.78 (d), 118.82 (d), 115.92 (s), 111.46 (d), 30.48 (N-CH_3).

Analysis calculated for $C_{32}H_{24}Br_2N_4O_2S_2$ requires:

C, 53.3; H, 3.4; N, 7.8; S, 8.9%.

Found: C, 53.1; H, 3.5; N, 7.7; S, 8.9%.

Compound 90 of Table 1

A solution of 4-methoxy-1-methyl-2-oxindole [VII: R_1 = 4-OMe, R_3 = Me] (1.20 g, 6.77 mmol) in 48% HBr/glacial AcOH (40 mL) was heated under reflux for 6 hours, then poured into water. The precipitate of crude phenol was filtered off, washed well with water and dried, then acetylated with Ac_2O/pyridine for 1 hour at 20°C. Solvents were removed under reduced pressure, and the residue was partitioned between EtOAc and 3N HCl. Chromatography of the organic residue on silica gel, eluting with EtOAc/petroleum ether gave 4-acetoxy-1-methyl-2-oxindole [VII: R_1 = 4-OAc, R_3 = Me] (75% yield); mp 109-111°C.

^{1}H NMR ($CDCl_3$): δ 7.30 (1H, dd, *J* = 8.2, 7.7 Hz, H-6), 6.78 (1H, d, *J* = 8.2 Hz, H-7), 6.71 (1H, d, *J* = 7.7 Hz, H-5), 3.41 (2H, s, H-3), 3.22 (3H, s, N-CH_3), 2.32 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 174.26 (C-2), 168.30 (O<u>C</u>OCH_3), 164.71 (s), 146.58 (s), 129.12, 116.62 (s), 115.83 (d), 105.90 (d), 33.74 (C-3), 26.51 (N-CH_3), 20.83 (COO<u>C</u>H_3).

Analysis calculated for $C_{11}H_{11}NO_3$ requires:

C, 64.4; H, 5.4; N, 6.8%.

Found: C, 64.3; H, 5.4; N, 7.0%.

Reaction of this with P_2S_5 as above gave 4-acetoxy-1-methyl-2-indolinethione [IX: R_1 = 4-OAc, R_3 = Me] (94% yield); mp 156°C.

^{1}H NMR ($CDCl_3$): δ 7.35 (1H, dd, *J* = 8.2, 7.9 Hz, H-6), 6.90 (1H, d, *J* = 8.2 Hz, H-7), 6.86 (1H, d, *J* = 7.9 Hz, H-5), 4.00 (2H, s, H-3), 3.61 (3H, s, N-CH_3), 2.32 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 200.75 (C-2), 168.14 (O<u>C</u>OCH_3), 148.30 (s), 146.27 (s), 129.44 (d), 121.18 (s), 117.69 (d), 107.32 (d), 47.09 (C-3), 31.57 (N-CH_3), 20.81 (COO<u>C</u>H_3).

Analysis calculated for $C_{11}H_{11}NO_2S$ requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.4; H, 5.2; N, 6.6; S, 14.5%.

Reaction with phenyl isocyanate as above gave 2,2'-dithiobis[N-phenyl 4-acetoxy-1-methylindolyl-3-carboxamide] (**90**) [V: R_1 = 4-OAc, R_2 = CONHPh, R_3 = Me] (31%); mp 194°C.

^{1}H NMR ($(CD_3)_2SO$): δ 9.92 (1H, s, CONH), 7.34-7.27 (4H, m, H-5,7,2',6'), 7.14 (2H, dd, *J* = 7.8, 7.6 Hz, H-3',5'), 6.98 (1H, t, *J* = 7.8 Hz, H-5'), 6.89 (1H, dd, *J* = 8.0, 7.8 Hz, H-5), 3.66 (3H, s, NCH_3), 1.95 (3H, s, OCH_3).

^{13}C NMR: δ 168.57 (<u>C</u>ONHPh), 162.09 (O<u>C</u>OCH_3), 142.91 (s), 139.20 (s), 138.75 (s), 129.01 (s), 128.38 (d),

124.56 (d), 123.14 (d), 119.23 (s), 118.38 (d), 117.70 (s), 113.94 (d), 108.70 (d), 30.39 (N-CH_3), 20.32 (COO$\underline{C}H_3$).

Analysis calculated for $C_{36}H_{30}N_4O_6S_2$ requires: 679.1685.

Found: $[M + H]^+$ 679.1705 (FABMS).

<u>Compound 91 of Table 1</u>

Similar demethylation/acetylation of 5-methoxy-1-methyl-2-oxindole [VII: R_1 = 5-OMe, R_3 = Me] gave 5-acetoxy-1-methyl-2-oxindole [VII: R_1 = 5-OAc, R_3 = Me] (70% yield); mp (EtOAc/petroleum ether) 104-106°C.

^{1}H NMR ($CDCl_3$): δ 7.01 (1H, br s, H-4), 7.00 (1H, dd, J = 9.1, 2.4 Hz, H-6), 3.53 (2H, s, H-3), 3.20 (3H, s, N-CH_3), 2.30 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 174.79 (C-2), 169.96 (O$\underline{C}$OCH_3), 146.08 (s), 142.96 (s), 125.50 (s), 120.84 (d), 118.54 (d), 108.25 (d), 35.89 (C-3), 26.30 (N-CH_3), 21.04 (OCO$\underline{C}H_3$).

Analysis calculated for $C_{11}H_{11}NO_3$ requires: C, 64.4; H, 5.4; N, 6.8%.

Found: C, 64.4; H, 5.4; N, 6.8%.

Reaction of this with P_2S_5 as above gave 5-acetoxy-1-methyl-2-indolinethione [IX: R_1 = 5-OAc, R_3 = Me] (86% yield); mp 134-135.5°C.

^{1}H NMR ($CDCl_3$): δ 7.06 (2H, br s, H-4,6), 6.93 (1H, d, J = 8.6 Hz, H-7), 4.08 (2H, s, H-3), 3.60 (3H, s, N-CH_3), 2.31 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 200.86 (C-2), 169.62 (O$\underline{C}$OCH_3) 147.62 (s), 144.14 (s), 130.10 (s), 120.97 (d), 117.99 (d), 109.62 (d), 48.79 (C-3), 31.24 (N-CH_3), 20.94 (OCO$\underline{C}H_3$).

Analysis calculated for $C_{11}H_{11}NO_2S$ requires: C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.6; H, 5.2; N, 6.2; S, 14.6%.

Reaction with phenyl isocyanate as above gave 2,2'-dithiobis[*N*-phenyl-5-acetoxy-1-methylindolyl-3-carboxamide] (91) [V: R_1 = 5-OAc, R_2 = CONHPh, R_3 = Me], (45% yield); mp 147-150°C.
^{1}H NMR ($(CD_3)_2SO$): δ 9.60 (1H, br, CONH), 7.54 (1H, d, *J* = 1.9 Hz, H-4), 7.42 (1H, d, *J* = 8.9 Hz, H-7), 7.23 (2H, d, *J* = 7.8 Hz, H-2',6'), 7.17 (2H, dd, *J* = 7.8, 7.1 Hz, H-3',5'), 7.06 (1H, dd, *J* = 8.9, 1.9 Hz, H-6), 6.98 (1H, t, *J* = 7.1 Hz, H-4), 3.66 (3H, s, NCH_3), 2.29 (3H, s, $OCOCH_3$).
^{13}H NMR: δ 169.52 (CONH), 161.18 ($O\underline{C}OCH_3$), 145.27 (s), 138.49 (s), 135.41 (s), 128.31 (d), 125.46 (s), 122.94 (d), 119.15 (d), 112.82 (d), 111.43 (d), 30.26, ($N-CH_3$), 20.80 ($OCO\underline{C}H_3$).
Analysis calculated for $C_{36}H_{30}N_4O_6S_2 \cdot 0.5H_2O$ requires:
C, 62.9; H, 4.5; N, 8.2; S, 9.3%.
Found: C, 63.1; H, 4.6; N, 8.2; S, 9.5%.

Compound 92 of Table 1

A stirred suspension of the 5-acetoxydisulfide (91) (0.25 g, 0.37 mmol) in MeOH (15 mL) was treated with $NaBH_4$ (0.05 g, 1.32 mmol) at 20°C for 10 minutes. Aqueous 3N KOH (2 mL) was then added, and after a further 15 minutes the solution was diluted with water and extracted with CH_2Cl_2. The resulting oil was immediately dissolved in MeOH (3 mL) and mixed with H_2O_2 (0.10 mL of 35%). The solution was chilled at -30°C for 48 hours and then filtered to yield 2,2'-dithiobis(*N*-phenyl-5-hydroxy-1-methylindole-3-carboxamide) (92) [V: R_1 = 5-OH, R_2 = CONHPh, R_3 = Me] (41 mg, 19%); mp 185-187°C.
^{1}H NMR ($(CD_3)_2SO$): δ 9.50 (1H, s, CONH), 9.15 (1H, br, OH), 7.32 (2H, d, *J* = 7.8 Hz, H-2',6'), 7.27 (1H, d, *J* = 8.9 Hz, H-7), 7.19 (1H, d, *J* = 2.3 Hz, H-4), 7.18

(2H, dd, J = 7.8, 7.4 Hz, H-3',5'), 6.99 (1H, t, J = 7.4 Hz, H-4'), 6.83 (1H, dd, J = 8.9, 2.3 Hz, H-6), 3.51 (3H, s, N-CH_3).

Analysis calculated for $C_{32}H_{26}N_4O_4S_2 \cdot H_2O$ requires:

C, 64.6; H, 4.4; N, 9.4%.

Found: C, 62.7; H, 4.6; N, 9.1%.

Compound 93 of Table 1

Similar demethylation/acetylation of 6-methoxy-1-methyl-2-oxindole [VII: R_1 = 6-OMe, R_3 = Me] gave 6-acetoxy-1-methyl-2-oxindole [VII: R_1 = 6-OAc, R_3 = Me] (81% yield); mp 119-121°C.

^{1}H NMR ($CDCl_3$): δ 7.22 (1H, d, J = 7.9 Hz, H-4), 6.74 (1H, dd, J = 7.9, 2.1 Hz, H-5), 6.59 (1H, d, J = 2.1 Hz, H-7), 3.49 (2H, s, H-3), 3.18 (3H, s, N-CH_3), 2.31 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 175.28 (C-2), 169.57 ($O\underline{C}OCH_3$), 150.74 (s), 146.23 (s), 124.83 (d), 121.81 (s), 115.00 (d), 102.68 (d), 35.33 (C-3), 26.27 (N-CH_3), 21.09 ($OCO\underline{C}H_3$).

Analysis calculated for $C_{11}H_{11}NO_3$ requires:

C, 64.4; H, 5.4; N, 6.8%.

Found: C, 64.5; H, 5.5; N, 6.9%.

Reaction of this with P_2S_5 as above gave 6-acetoxy-1-methyl-2-indolinethione [IX: R_1 = 6-OAc, R_3 = Me] (91% yield); mp 131-133°C.

^{1}H NMR: δ ($CDCl_3$) 7.27 (1H, d, J = 8.0 Hz, H-4), 6.87 (1H, dd, J = 8.0, 1.9 Hz, H-5), 6.75 (1H, d, J = 1.9 Hz, H-7), 4.08 (2H, s, H-3), 3.58 (s, N-CH_3), 2.33 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 202.18 (C-2), 169.44 ($O\underline{C}OCH_3$), 150.80 (s), 147.57 (s), 126.38 (s), 124.32 (d), 117.05 (d), 104.06 (d), 48.62 (C-3), 31.33 (N-CH_3), 21.09 ($OCO\underline{C}H_3$).

Analysis calculated for $C_{11}H_{11}NO_2S$ requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.4; H, 5.2; N, 6.1; S, 14.3%.

Reaction with phenyl isocyanate as above gave 2,2'-dithiobis[*N*-phenyl-6-acetoxy-1-methylindolyl-3-carboxamide] (93) [V: R_1 = 6-OAc, R_2 = CONHPh, R_3 = Me] (53%); mp 219-222°C.

^{1}H NMR ($(CD_3)_2SO$): δ 9.71 (1H, br s, CONH), 7.78 (1H, d, *J* = 8.7 Hz, H-4), 7.27 (3H, m, H-2',6'), 7.18 (2H, dd, *J* = 8.2, 7.3 Hz, H-3',5'), 6.99 (1H, t, *J* = 7.3 Hz, H-4'), 6.95 (1H, dd, *J* = 8.7, 1.8 Hz, H-5), 3.60 (3H, s, NCH_3), 2.32 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 169.31 (<u>C</u>ONHPh), 161.23 (O<u>C</u>OCH$_3$), 147.99 (s), 138.54 (s), 137.66 (s), 128.29 (d), 123.13 (s), 122.98 (d), 121.48 (d), 119.38 (d), 118.73 (s), 116.34 (d), 103.76 (d), 30.17 (N-CH_3), 20.81 (OCO<u>C</u>H$_3$).

Analysis calculated for $C_{36}H_{30}N_4O_6S_2$ requires:

C, 63.7; H. 4.5; N, 8.3; S, 9.4%.

Found: C, 63.7; H, 4.4; N, 8.2; S, 9.8%.

<u>Compound 94 of Table 1</u>

Similar treatment of the 6-acetoxydisulfide (93) gave 2,2'-dithiobis(6-hydroxy-1-methyl-*N*-phenyl-1H-indole-3-carboxamide) (94) [V: R_1 = 6-OH, R_2 = CONHPh, R_3 = Me]; mp 185-187°C (dec).

^{1}H NMR ($(CD_3)_2SO$): δ 10.01, 9.43 (2H, 2s, OH and CONH), 7.76 (1H, d, *J* = 7.9 Hz, H-4), 7.35 (2H, d, *J* = 7.6 Hz, H-2',6'), 7.31 (1H, d, *J* = 2.2 Hz, H-7), 7.10 (2H, dd, *J* = 7.6, 7.4 Hz, H-3',5'), 6.95 (1H, t, *J* = 7.4 Hz, H-4'), 6.71 (1H, dd, *J* = 7.9, 2.2 Hz, H-5), 3.58 (3H, s, NCH_3).

Analysis calculated for $C_{32}H_{26}N_4O_4S_2$ requires:

595.1474.

Found: $[M + H]^+$ 595.1483 (FABMS).

Compound 95 of Table 1

Similar demethylation/acetylation of 7-methoxy-1-methyl-2-oxindole [VII: R_1 = 7-OMe, R_3 = Me] gave 7-acetoxy-1-methyl-2-oxindole [VII: R_1 = 7-OAc, R_3 = Me] (68% yield); mp 95-97°C.

^{1}H NMR ($CDCl_3$): δ 7.12 (1H, dd, J = 7.1, 1.0 Hz, H-6), 7.01 (1H, dd, J = 8.4, 7.1 Hz, H-5), 6.96 (1H, dd, J = 8.4, 1.0 Hz, H-4), 3.54 (2H, s, H-3), 3.34 (3H, s, N-CH_3), 2.35 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 174.88 (C-2), 169.57 (O$\underline{C}$OCH_3), 136.11 (s), 134.24 (s), 126.73 (s), 123.02 (d), 122.60 (d), 122.18 (d), 35.68 (C-3), 28.17 (N-CH_3), 20.89 (OCO$\underline{C}H_3$).

Analysis is calculated for $C_{11}H_{11}NO_3$ requires:
C, 64.4; H, 5.4; N, 6.8%.
Found: C, 64.5; H, 5.5; N, 6.7%.

Reaction of this with P_2S_5 as above gave 7-acetoxy-1-methyl-2-indolinethione [IX: R_1 = 7-OAc, R_3 = Me] (85% yield); mp 133-135°C.

^{1}H NMR ($CDCl_3$): δ 7.17 (1H, d, J = 7.9 Hz, H-6), 7.14 (1H, dd, J = 8.0, 7.9 Hz, H-5), 7.01 (1H, d, J = 8.0 Hz, H-4), 4.13 (2H, s, H-3), 3.78 (3H, s, N-CH_3), 2.39 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 202.00 (C-2), 169.22 (O$\underline{C}$OCH_3), 137.53 (s), 134.33 (s), 131.42 (s), 124.78 (d), 123.23 (d), 121.69 (d), 49.20 (C-3), 33.67 (N-CH_3), 20.97 (OCO$\underline{C}H_3$).

Analysis calculated for $C_{11}H_{11}NO_2S$ requires:
C, 59.7; H, 5.0; N, 6.3; S, 14.5%.
Found: C, 59.4; H, 5.2; N, 6.2; S, 14.2%.

Reaction with phenyl isocyanate as above gave 2,2'-dithiobis[*N*-phenyl-7-acetoxy-1-methylindolyl-3-carboxamide] (95) [V: R_1 = 7-OAc, R_2 = CONHPh, R_3 = Me]; mp 212-214.5°C.

^{1}H NMR ($(CD_3)_2SO$): δ 10.28 (1H, br, CONH), 7.72 (1H, d, J = 7.8 Hz, H-4), 7.44 (2H, d, J = 7.8 Hz, H-2',6'),

7.23 (2H, dd, J = 8.1, 7.8 Hz, H-3',5'), 7.11 (1H, dd, J = 7.8, 7.7 Hz, H-5), 7.01 (2H, m, H-6, H-4'), 3.68 (3H, s, N-CH_3), 2.35 (3H, s, $OCOCH_3$).

^{13}C NMR: δ 169.49 (CONHPh), 161.36 ($OCOCH_3$), 138.75 (s), 135.92 (s), 129.43 (s), 128.80 (s), 128.43 (d), 128.0 (s), 123.13 (d), 121.21 (d), 119.35 (d), 118.50 (d), 118.16 (d), 31.84 ($OCOCH_3$), 20.68 (N-CH_3).

Analysis calculated for $C_{36}H_{30}N_4O_6S_2 \cdot 0.5H_2O$ requires:

C, 62.9; H, 4.5; N, 8.2; S, 9.3%.

Found: C, 62.9; H, 4.5; N, 7.8; S, 9.6%.

Compound 96 of Table 1

Reaction of **96** as above with $NaBH_4$ followed by 3N KOH gave, after reoxidation, 2,2'-dithiobis(*N*-phenyl-7-hydroxy-1-methylindole-3-carboxamide) (**96**) [V: R_1 = 7-OH, R_2 = CONHPh, R_3 = Me] (81% yield); mp 207°C (dec).

^1H NMR ($(CD_3)_2SO$): δ 9.94, 9.63 (each 1H, 2s, CONH and ArOH), 7.33 (1H, d, J = 8.0 Hz, H-2',6'), 7.23 (1H, d, J = 8.0 Hz, H-4), 7.18 (2H, dd, J = 8.0, 8.0 Hz, H-3',5'), 6.99 (1H, t, J = 8.0 Hz, H-4'), 6.91 (1H, dd, J = 8.0, 7.5 Hz, H-5), 6.65 (1H, d, J = 7.5 Hz, H-6), 3.89 (3H, s, N-CH_3).

^{13}C NMR: δ 161.89 (CONH), 144.46 (s), 138.72 (s), 128.30 (d), 127.74 (s), 127.57 (s), 122.98 (d), 121.76 (d), 119.46 (d), 119.36 (s), 119.32 (s), 111.57 (d), 108.85 (d), 32.84 (N-CH_3).

Analysis calculated for $C_{32}H_{26}N_4O_4S_2$ requires:

C, 64.3; H, 4.4; N, 9.4; S, 10.8%.

Found: C, 64.2; H, 4.4; N, 9.3; S, 10.9%.

Compound 97 of Table 1

Similarly was prepared, from 1-methyl-2-indolinethione and methyl isocyanate, bis[N-methyl 1-methylindolyl-3-carboxamide-(2)]-disulfide [V: R_1 = H, R_2 = CONHMe, R_3 = Me] (97) (18% yield); mp 162-165°C.
^{1}H NMR ($CDCl_3$): δ 8.07 (1H, d, J = 8.0 Hz, H-4), 7.40-7.20 (3H, m, H-5, H-6, H-7), 6.31 (1H, br, CONH), 3.82 (3H, s, NCH_3), 2.13 (3H, d, J = 5.0 Hz, $CONHCH_3$).
^{13}C NMR ($CDCl_3$): δ 173.29 (CONH), 128.34 (s), 125.28, 122.31, 122.02, 120.0 (s), 116.5 (s), 113.2 (s), 110.06, 30.26 (N-CH_3), 25.68 ($CONHCH_3$).

Alternate Preparation of Compound 97 of Table 1

A mixture of 20 g (136 mmol) of 1-methyl-2-indolinone and 250 mL of dichloroethane was sealed in a 500 mL stainless steel autoclave. The reactor was cooled to less than -10°C and 60 g of phosgene was distilled into the vessel. The reactor was sealed and heated to 80°C while rocking. After 1 hour, the reactor was cooled to room temperature, vented, and purged with nitrogen. The reactor was opened and the solution was rinsed out with fresh dichloromethane. The dichloroethane solution from the rinsed reactor was concentrated to a purple solid. The solid was dissolved into 300 mL of dichloromethane and the solution was cooled in an ice bath. Into the cold solution was bubbled anhydrated methylamine at a moderate rate over a 50-minute period. The mixture was washed with water (2 x 300 mL) and brine, dried (Na_2SO_4), and concentrated to ca. 150 mL. The solution was purified by flash silica gel chromatography (7.5 x 13 cm bed) eluting with 1.6 L dichloromethane, 2 L 2%, then 2 L 5% acetone/dichloromethane, with

500 mL fractions collected. Impure early product fractions were combined, concentrated, and recrystallized from 40 mL ethanol/12 mL pet ether to give 3.04 g of 2-chloro-1-methylindole-3-N-methylcarboxamide [XXII: R_6 = H, R_7 = CH_3]; mp 148-151°C. Pure product fractions were combined and concentrated to give 16.41 g of additional product as a pale yellow solid; mp 150-151°C. Total yield = 19.45 g (64%).

Reaction of 9.30 g (41.8 mmol) of the above carboxamide was carried out with 129.5 mmol of MeSLi in 36 mL of DMA. After heating at 60°C for 7 hours, the clear amber solution was cooled in an ice bath and treated slowly with 150 mL of 5% aqueous HCl. The resultant suspension was diluted with ca. 150 mL of dichloromethane, and the mixture was stirred for 1 hour. The layers were separated, and the aqueous phase was extracted twice more. The combined organic extracts were washed with water (3 x 200 mL), then brine, dried $MgSO_4$, and concentrated to a residue that was pumped at 0.05 mm for 1 hour to leave 12.5 g of an orange solid. The solid was suspended into 100 mL of HOAc and 50 mL of water, and with vigorous stirring the suspension was treated with 12.85 g of sodium perborate. The thick suspension was stirred for ca. 30 minutes, then filtered using 10% methanol in water to aid in the transfer. The solids were washed well with water, then with ether, and air dried. Further drying at 200 mm/65°C/overnight over P_2O_5 afforded 6.38 g (70%) of pure bis[N-methyl 1-methylindolyl-3-carboxamide-(2)]disulfide (97) [V: R_2 = $CONHCH_3$]; mp 186-187°C.

Compound 98 of Table 1

Similarly was prepared, from 1-methyl-2-indolinethione and benzyl isocyanate, bis[N-benzyl 1-methylindolyl-3-carboxamide-(2)]disulfide [V: R_1 = H, R_2 = $CONHCH_2Ph$, R_3 = Me] (98) (0.12 g, 22%); mp 145-147°C.

^{1}H NMR ($CDCl_3$): δ 8.13 (1H, d, J = 8.1 Hz, H-4), 7.38 (1H, t, J = 7.4 Hz, H-6), 7.31-7.20 (6H, m, H-5 and CH_2<u>Ph</u>), 7.11 (1H, d, J = 7.4 Hz, H-7), 6.60 (1H, br, CONH), 3.75 (2H, br, COC<u>H_2</u>Ph), 3.64 (3H, s, N-CH_3).

^{13}C NMR ($CDCl_3$): δ 163.42 (<u>C</u>ONH), 138.37 (s), 128.59, 128.54 (s), 127.63 (s), 127.52, 127.40 (s), 127.20, 126.40 (s), 125.39, 122.52, 122.32, 110.30 (C-7), 42.94 (CH_2Ph), 30.24 (N-CH_3).

Analysis calculated for $C_{34}H_{30}N_4O_2S_2$ requires:
C, 69.1; H, 5.2; N, 9.5; S, 10.8%.
Found: C, 68.6; H, 5.3; N, 9.5; S, 10.6%.

EXAMPLE E

Preparation of Compounds 19 and 83 of Table 1 by the Method of Scheme 4

A mixture of 2-amino-3-methylpyridine (43.28 g, 0.4 mol) and benzotriazole (47.65 g, 0.4 mol) in EtOH (500 mL) was treated over 5 minutes with formaldehyde (32.2 g of 37% solution, 0.4 mol). The mixture was stirred at 20°C overnight, then cooled and filtered to give 2-[(1-benzotriazolyl)methyl]-3-methyl pyridine (30 g, 31%). A sample was crystallized from EtOH; mp 175-177°C.

^{1}H NMR ($CDCl_3$): δ 8.10 (1H, d, J = 5 Hz, H-8), 8.10 and 8.00 (2H, 2d, J = 8 Hz, H-4',7'), 7.45 and 7.33 (2H, 2t, J = 8 Hz, H-5',6'), 7.25 (1H, d, J = 7 Hz, H-4), 6.54 (1H, dd, J = 7.5 Hz, H-5), 6.47 (2H, d,

J = 7 Hz, CH_2), 5.38 (1H, t, J = 7 Hz, NH), 2.07 (3H, s, CH_3).

Crude 2-[(1-benzotriazolyl)methyl]-3-methylpyridine (30 g, 125 mmol) was suspended in dioxan (400 mL) and treated with NaBH4 (5 g, 130 mmol). The mixture was heated under reflux for 8 hours, then the majority of the solvent was removed under reduced pressure. The residue was partitioned between toluene and water, and the organic layer was washed successively with dilute NaOH solution and water, and dried. Removal of the solvent gave 2-methylamino-3-methylpyridine as an oil (12.8 g, 84%).

^{1}H NMR ($CDCl_3$): δ 8.04 (1H, d, J = 5.1 Hz,H, H-6), 7.19 (1H, d, J = 7.1 Hz, H-4), 6.50 (1H, dd, J = 7.1, 5.1 Hz, 5-H), 4.15 (1H, m, NH), 3.03 (3H, d, J = 4.5 Hz, CH_3N), 2.06 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$): δ 157.3 (C-2), 145.0 (C-8), 136.1 (C-4), 116.4 (C-3), 111.9 (C-5), 28.3 (CH_2) and 16.5 (CH_3).

A solution of the above pyridine (6.1 g, 50 mmol) in dry THF (150 mL) was cooled to -78°C under dry N_2, and n-BuLi (19.6 mL of a 2.5 M solution in hexanes, 50 mmol) was added dropwise, followed by t-BuLi (32 mL of a 1.7 M in pentane, 55 mmol). The resulting mixture was allowed to warm to -20°C and maintained at that temperature for 30 minutes before being recooled to -78°C and treated with dry CO_2 gas until the mixture was decolorized. After warming to 20°C, the mixture was acidified with dilute HCl, and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (100 mL) containing p-TsOH (100 mg), heated under reflux for 3 hours to effect ring closure, and neutralized with aqueous ammonia. Solvent was then removed, and the residue was worked up in EtOAc to give

an oil, which was extracted with hot hexane, charcoaled, and filtered through celite. Concentration of the solution and cooled, gave 1-methyl-7-aza-2-indolinone(1,3-dihydro-1-methyl-2H-pyrrolo-(2,3-bipyridin-2-one) [VII: R_1 = 7-aza, R_3 = Me] (1.2 g, 15%); mp (hexane) 94-96°C.
^{1}H NMR ($CDCl_3$): δ 8.15 (1H, d, J = 5.3 Hz, H-8), 7.48 (1H, d, J = 7.2 Hz, H-4), 8.94 (1H, dd, J = 7.2, 5.3 Hz, H-5), 3.53 (2H, s, CH_2), 3.29 (3H, s, CH_3).
^{13}C NMR ($CDCl_3$): δ 174.1 (C-2), 158.1 (C-7a), 146.6 (C-8), 131.3 (C-4), 119.0 (C-3a), 117.8 (C-5), 34.6 (CH_2), 25.1 (CH_3).

P_2S_5 (3.80 g, 8.10 mmol) was added to a vigorously stirred suspension of Na_2CO_3 (0.88 g, 8.10 mmol) in THF (30 mL). After the mixture had become homogeneous (ca. 15 minutes), a solution of 1-methyl-7-aza-2-indolinone [VII: R_1 = 7-aza, R_3 = Me] (1.00 g) in THF (10 mL) was added and stirring was continued for 18 hours at 20°C. Solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. Workup of the organic layer, and chromatography of the residue on silica gel (elution with EtOAc/petroleum ether (1:5)) gave 1-methyl-7-aza-2-indolinethione [IX: R_1 = 7-aza, R_3 = Me] (0.81 g, 73%); mp (EtOAc/petroleum ether) 130-133°C.
^{1}H NMR ($CDCl_3$): δ 8.28 (1H, dd, *J* = 5.2, 0.6 Hz, H-6), 7.57 (1H, dd, *J* = 7.3, 0.6 Hz, H-4), 7.07 (1H, dd, *J* = 7.3, 5.2 Hz, H-5), 4.06 (2H, s, H-3), 3.66 (3H, s, N-CH_3).
^{13}C NMR: δ 201.70 (C-2), 159.21 (s), 147.22 (d), 131.39 (d), 123.20 (s), 119.34 (d), 46.98 (C-3), 30.02 (N-CH_3).

Analysis calculated for $C_8H_8N_2S$ requires:

C, 58.5; H, 4.9; N, 17.1; S, 19.5%.

Found: C, 58.3; H, 4.9; N, 17.0; S, 19.8%.

A solution of the above thione (0.70 g, 4.26 mmol) in THF (5 mL) was added dropwise over 5 minutes under N_2 to an ice-cooled suspension of NaH (0.2 g of a 60% w/w dispersion in oil, 6.11 mmol). After gas evolution had ceased (5 minutes), phenyl isocyanate (0.47 mL, 4.25 mmol) was added, and stirring was continued for 1 hour at 20°C. Aqueous 1N HCl was then added, and the mixture was extracted with EtOAc. The organic layer was worked up, and the residue was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) and EtOAc gave foreruns, while elution with EtOAc/MeOH (10:1) gave N-phenyl (1-methyl-7-aza-2-thioxo-3-indolinyl)carboxamide (19) [IV: R_1 = 7-aza, R_2 = CONHPh, R_3 = Me] as a fluorescent green solid (0.67 g, 55% yield); mp (after trituration with MeOH) 162-164°C (dec).

^{1}H NMR ($(CD_3)_2SO$): δ 12.46 (1H, s, CONH), 8.68 (1H, dd, J = 7.7, 1.0 Hz, H-6), 8.02 (1H, d, J = 6.0 Hz, H-4), 7.72 (2H, d, J = 8.4 Hz, ArH), 7.36-7.29 (4H, m, ArH), 7.01 (1H, t, J = 7.3 Hz, ArH), 3.80 (3H, s, N-CH_3).

^{13}C NMR: δ 66.96 (C-2), 163.59 (CONH), 140.77 (s), 139.81 (s), 129.29 (d), 128.85 (d), 127.21 (s), 126.84 (d), 122.16 (d), 118.65 (d), 115.92 (d), 48.57 (C-3), 29.18 (N-CH_3).

Analysis calculated for $C_{15}H_{13}N_3O_2S \cdot CH_3OH$ requires:

C, 60.9; H, 5.4; N, 13.3; S, 10.2%.

Found: C, 60.6; H, 5.4; N, 13.4; S, 10.3%.

A solution of sodium perborate (0.50 g, 5.00 mmol) in water (25 mL) was added to a vigorously stirred suspension of the above 7-aza compound (19) (0.50 g,

176 mmol) in glacial AcOH (50 mL). After 1 hour the solid was filtered off, washed sequentially with water and Et_2O, and dried to give 2,2'-dithiobis[*N*-phenyl-1-methyl-7-azaindolyl-3-carboxamide] [V: R_1 = 7-aza, R_2 = CONHPh, R_3 = Me] (83) (100%); mp 197-198°C.
^1H NMR ($(CD_3)_2SO$): δ 9.49 (1H, s, CONH), 8.36 (1H, dd, *J* = 4.5, 1.5 Hz, H-6), 8.14 (1H, dd, *J* = 7.9, 1.5 Hz, H-4), 7.19 (1H, dd, *J* = 7.9, 4.5 Hz, H-5), 7.16-7.09 (4H, m, ArH), 6.98 (1H, m, ArH), 3.75 (3H, s, N-CH_3).
^{13}C NMR: δ 160.42 (CONH), 147.58 (s), 145.99 (d), 138.29 (s), 129.86 (s), 129.62 (d), 128.25 (d), 123.05 (d), 119.23 (d), 118.09 (s), 117.76 (d), 117.57 (s), 28.61 (N-CH_3).
Analysis calculated for $C_{30}H_{24}N_6O_2S_2 \cdot 2.5H_2O$ requires:
C, 59.1; H, 4.8; N, 13.8; S, 10.5%.
Found: C, 59.1; H, 4.2; N, 13.8; S, 10.5%.

EXAMPLE F

Preparation of Compound 99 of Table 1 by the Method Outlined in Scheme 5

A solution of 2-[(4-methylphenylsulfonyl)methyl]-aniline [XII: R_1 = H, R_2 = Me, X = 4-methylphenyl] (Le Corre M, Hercouet A, Le Stanc Y, Le Baron H, Tetrahedron 1985;22:5313) in dry THF (60 mL), under N_2, was cooled to -78°C and n-butyllithium (9.6 mL, 2.5 M solution in hexanes) was added dropwise. The mixture was allowed to warm to -10°C to give a deep red colored solution which was recooled to -78°C after 30 minutes. CS_2 (3 mL, 5 mmol) was added rapidly, and the mixture was allowed to warm slowly to 20°C. The solvent was removed under vacuum and the residue was diluted with water, and acidified with 2 M HCl. After stirring at 20°C for 3 hours, the solution was extracted with EtOAc and dried (Na_2SO_4). The solvent was removed, and

chromatography of the residue on SiO_2 (CH_2Cl/EtOAc, 9:1) gave bis[3-(4-methylphenylsulfonyl)-2-indolyl]-disulfide [XIII: R_1 = H, R_2 = Me, X = 4-methylphenyl] (99) (0.2 g, 7% yield); mp (benzene) 230-233°C.
^{1}H NMR ($CDCl_3$): δ 8.06 (1H, m, NH), 7.91 (3H, m, H-4, H-2, and H-4'), 7.45 (1H, m, H-6), 7.21 (4H, m, H-5, H-7, H-3', and H-5'), 2.33 (3H, s, CH_3).
^{13}C NMR ($CDCl_3$): δ 144.1, 140.0, 136.6, 134.0, 129.9 (CH), 126.4 (CH), 125.4, 124.5 (CH), 122.8 (CH), 119.1 (CH), 115.1, 112.2 (CH), and 21.5 (CH_3).
Analysis calculated for $C_{30}H_{24}N_2O_4S_4 \cdot 0.2(C_6H_6)$ requires: C, 60.4; H, 4.1; N, 5.5; S, 20.7%.
Found: C, 60.7; H, 4.4; N, 4.9; S, 21.1%.

EXAMPLE G

Preparation of Compounds 24 and 100 of Table 1 by the Method Outlined in Scheme 6

A stirred solution of benzoyl chloride (from benzoic acid, 0.45 g, 3.68 mmol) in Me_2CO (20 mL) was treated dropwise at 0°C with a solution of NaN_3 (0.26 g, 3.98 mmol) in water (2 mL). After 15 minutes the solution was partitioned between water and benzene, and the organic layer was washed well with $NaHCO_3$ and worked up to give crude phenacyl azide, which was used directly.

A solution of 1-methyl-2-indolinethione (0.50 g, 3.06 mmol) in dry THF (3 mL) was added dropwise at 20°C under N_2 to a stirred suspension of NaH (0.13 g of a 60% w/w suspension in mineral oil, 3.37 mmol) in THF (2 mL). After gas evolution had ceased (5 minutes), a solution of the above phenacyl azide in THF (2 mL) was added dropwise, and the mixture was stirred at 20°C for 1 hour, then poured into 6N HCl and extracted with EtOAc. The residue from the organic layer was

chromatographed on silica gel. Elution with CH_2Cl_2/petroleum ether (3:7) gave foreruns, and elution with CH_2Cl_2/petroleum ether (2:3) gave 3-benzoyl-1-methyl-2-indolinethione [XV: R_1 = H, R_3 = Me, R_5 = C6H5] (**24**) (0.31 g, 38%); mp (trituration from MeOH) 132-134°C.

^{1}H NMR ($CDCl_3$): δ 15.83 (1H, s, SH), 7.68-7.53 (5H, m, COPh), 7.21 (1H, dd, J = 8.1,7.3 Hz, H-5), 7.11 (1H, d, J = 8.1 Hz, H-4), 6.90 (1H, dd, J = 8.0, 7.3 Hz, H-6), 6.76 (1H, d, J = 8.0 Hz, H-7), 3.74 (3H, s, NCH_3).

^{13}C NMR ($CDCl_3$): δ 181.71 (<u>C</u>OPh), 175.09 (C-2), 141.42 (s), 134.87 (s), 131.29, 128.85, 128.37, 125.64 (4xd), 125.22 (s), 122.81, 120.31 (2xd), 111.77 (s), 109.129 (d), 29.57 (NCH_3).

Analysis calculated for $C_{16}H_{13}NOS$ requires:
C, 71.9; H, 4.9; N, 5.2; S, 12.0%.
Found: C; 71.6; H, 5.1; N, 6.2; S, 13.9%.

A solution of **24** (0.10 g, 0.37 mmol) in CH_2Cl_2 (20 mL) was treated dropwise at 20°C with a solution of I_2 (0.50 g) in CH_2Cl_2 (5 mL), until TLC indicated complete conversion (ca. 2 hours). The solution was concentrated to ca. 1 mL and chromatographed directly on silica gel. Elution with CH_2Cl_2 gave traces of I_2 and starting material, and further elution with CH_2Cl_2/MeOH (19:1) gave bis[3-benzoyl-1-methylindole-(2)]disulfide [XVI: R_1 = H, R_3 = Me, R_5 = C_6H_5] (**100**) (0.06 g, 61%); mp ($CHCl_3$/petroleum ether) 199-202°C.

^{1}H NMR (CD_3SOCD_3): δ 7.56 (1H, d, J = 8.4 Hz, H-4), 7.50 (1H, d, J = 8.1 Hz, H-7), 7.46 (dd, J = 8.1, 7.4 Hz, H-6), 7.35 (1H, dd, J = 8.4, 7.4 Hz, H-5), 7.19 (3H, m, H-2',4',6'), 6.92 (2H, d, J = 7.1 Hz, H-3',5'), 3.48 (3H, s, NCH_3).

^{13}C NMR (CD_3SOCD_3): δ 190.20 (<u>C</u>OPh), 140.05, 138.03, 132.75 (3xs), 131.60, 128.48, 127.88 (3xd), 126.00 (s),

124,78, 122.27 (2xd), 122.03 (s), 121.03, 111.20 (2xd), 30.37 (NCH_3).
Analysis calculated for $C_{32}H_{24}N_2O_2S_2$ requires:
C, 69.8; H, 4.8; N, 5.1; S, 11.6%.
Found: C, 70.3; H, 4.7; N, 5.2; S, 11.3%.

Compounds 25, 26, 101, and 102 of Table 1

Similar treatment of 1-methyl-2-indolinethione with 4-carbomethoxybenzoyl azide gave 3-(4'-carbomethoxybenzoyl)-1-methyl-2-indolinethione [XV: R_1 = H, R_3 = Me, R_5 = 4-$MeOOCC_6H_4$] (**26**) (68%); mp 164-166°C.
^1H NMR ($CDCl_3$): δ 15.85 (1H, s, SH), 8.23 (2H, d, J = 8.3 Hz, H-3',5'), 7.76 (2H, d, J = 8.3 Hz, H-2',6'), 7.23 (1H, dd, J = 8.0, 7.6 Hz, H-5'), 7.12 (1H, d, J = 7.6 Hz, H-4), 6.90 (1H, dd, J = 8.0, 7.9 Hz, H-6), 6.69 (1H, d, J = 7.9 Hz, H-7), 3.99 (3H, s, $COOCH_3$), 3.74 (3H, s, NCH_3).
^{13}C NMR ($CDCl_3$): δ 182.07 ($\underline{C}OAr$), 173.27 (C-2), 166.31 ($\underline{C}OOCH_3$), 141.59, 138.92, 132.51 (3xs), 130.11, 128.54, 126.04 (3xd), 124.76 (s), 123.00, 120.26 (2xd), 119.95 (s), 109.28 (d), 52.50 ($COO\underline{C}H_3$), 29.61 (NCH_3).
Analysis calculated for $C_{18}H_{15}NO_3S$ requires:
C, 66.4; H, 4.7; N, 4.3; S, 9.8%.
Found: C, 66.5; H, 4.7; N, 4.6; S, 9.8%.

Oxidation of **26** with I_2/CH_2Cl_2 as above gave bis[3-(4'-carbomethoxybenzoyl)-1-methylindole-(2)]-disulfide [XVI: R_1 = H, R_3 = Me, R_5 = 4-$MeOOCC_6H_4$] (**102**); mp ($CHCl_3$/petroleum ether) 200-203°C.
^1H NMR (CD_3SOCD_3): δ 7.74 (2H, d, J = 8.4 Hz, H-3',5'), 7.67 (1H, d, J = 8.0 Hz, H-4), 7.64 (1H, d, J = 8.4 Hz, H-7), 7.44 (1H, dd, J = 8.4, 8.0 Hz, H-6), 7.27 (1H, dd, J = 8.0, 8.0 Hz, H-5), 6.99 (2H, d, J = 8.4 Hz, H-2',6'), 3.91 (3H, s, $COOCH_3$), 3.51 (3H, s, NCH_3).

^{13}C NMR (CD_3SOCD_3): δ 189.31 (<u>C</u>OAr), 165.56 (<u>C</u>$OOCH_3$), 143.77, 137.98, 133.31, 131.61 (4xs), 128.50, 128.33 (2xd), 125.87 (s), 124.99, 122.62 (2xd), 121.27 (s), 121.09, 111.22 (2xd), 52.34 (COO<u>C</u>H_3), 30.33 (NCH_3).

Analysis calculated for $C_{36}H_{28}N_2O_6S_2$ requires:

C, 66.6; H, 4.4; N, 4.3; S, 9.9%.

Found: C, 66.2; H, 4.8; N, 4.4; S, 9.9%.

A suspension of **26** (0.1 g, 0.31 mmol) in MeOH (5 mL) containing 3N NaOH (2 mL) was stirred at 20°C for 3 hours, then concentrated to dryness. The residue was dissolved in water and acidified (concentrated HCl) to give 3-(4'-carboxybenzoyl)-1-methyl-2-indolinethione [XV: R_1 = H, R_3 = Me, R_5 = 4-$HOOCC_6H_4$] (**25**) (100%); mp 282°C (dec).

^1H NMR (CD_3SOCD_3/CD_3COCD_3): δ 15.90 (0.3H, br, SH), 13.00 (1H, br s, COOH), 8.26 (2H, d, J = 8.2 Hz, H-3',5'), 8.10 (0.6H, s, SH), 7.85 (2H, d, J = 8.2 Hz, H-2',6'), 7.40 (1H, d, J = 8.0 Hz, H-4), 7.29 (1H, dd, J = 8.0, 8.0 Hz, H-5), 6.98 (1H, dd, J = 8.0, 7.5 Hz, H-6), 6.68 (1H, d, J = 7.5 Hz, H-7), 3.77 (3H, s, NCH_3).

^{13}C NMR CD_3SOCD_3/CD_3COCD_3): δ 167.57, 167.50 (<u>C</u>OAr and <u>C</u>OOH), 142.40, 135.64, 134.55 (3xs), 130.86, 130.18, 129.13, 126.93 (4xd), 125.17 (s), 123.81, 120.68 (2xd), 112.39 (s), 110.82 (d), 29.94 (NCH_3).

Analysis calculated for $C_{17}H_{13}NSO_3 \cdot H_2O$ requires:

C, 64.6; H, 4.3; N, 4.4; S, 10.1%.

Found: C, 64.6; H, 4.4; N, 4.0; S, 9.6%.

Similar hydrolysis of **102** gave bis[3-(4'-carboxybenzoyl)-1-methylindole-(2)]disulfide [XVI: R_1 = H, R_3 = Me, R_5 = 4-$HOOCC_6H_4$] (**101**); mp ($CHCl_3$/petroleum ether) 241-246°C.

^1H NMR (CD_3SOCD_3): δ 12.62 (1H, br, COOH), 7.89 (3H, m, H-4 and H-3',5'), 7.74 (1H, d, J = 8.5 Hz, H-7),

7.58 (3H, m, H-6 and H-2′,6′), 7.36 (1H, m, H-5), 3.66 (3H, s, NCH_3).

Analysis calculated for $C_{34}H_{24}N_2O_6S_2 \cdot 0.5 \cdot H_2O$ requires:
C, 63.1; H, 4.2%.
Found: C, 63.1; H, 5.3%.

EXAMPLE H

Preparation of Compounds 104 and 105 of Table 1 by the Method Outlined in Scheme 7

A solution of monomethyl terephthalate [XVII: 4-COOMe] (1.32 g, 7.33 mmol) and DMF (1 drop) in $SOCl_2$ (30 mL) was heated under reflux for 45 minutes, before concentration to dryness under reduced pressure. The residue was dissolved in benzene and evaporated to dryness again. The crude acid chloride was dissolved in dry Me_2CO (20 mL), cooled to 0°C, and treated with a solution of NaN_3 (0.52 g, 8.00 mmol) in water (3 mL). After 20 minutes the solution was diluted with water, extracted with CH_2Cl_2, and worked up to give the crude acyl azide [XVIII: 4-COOMe], which was immediately dissolved in dry toluene (25 mL) and heated under reflux under N_2 for 2 hours. Concentration to dryness under reduced pressure afforded the isocyanate [XIX: 4-COOMe] which was used directly.

A solution of 1-methyl-2-indolinethione [IV: R_1,R_2 = H, R_3 = CH_3] (1.00 g, 6.13 mmol) in THF (2 mL) was added under N_2 to a suspension of NaH (0.26 g of 60% w/w dispersion in mineral oil, 6.50 mmol) in THF (15 mL). After gas evolution had ceased (5 minutes), a solution of the above crude isocyanate in THF (10 mL) was added, and the solution was stirred at 20°C for a further 1 hour. The mixture was acidified with 3N HCl, extracted with EtOAc and

worked up to give an oily solid. Chromatography on silica gel, eluting with EtOAc, afforded a greenish solid. This was dissolved in MeOH and treated with 30% H_2O_2 (0.20 mL), and the resulting yellow precipitate was filtered off and washed well with MeOH to give 2,2'-dithiobis[*N*-(4'-carbomethoxy)phenyl-1-methylindolyl-3-carboxamide] **(104)** [XX: R = 4-COOMe] (0.74 g, 35%); mp 184-186°C.

^{1}H NMR ($(CD_3)_2SO$): δ 9.87 (1H, br, CONH), 7.80 (1H, d, *J* = 8.0 Hz, H-4), 7.74 (2H, d, *J* = 8.7 Hz, H-2',6'), 7.37 (1H, d, *J* = 8.3 Hz, H-7), 7.32 (2H, d, *J* = 8.7 Hz, H-3',5'), 7.26 (1H, dd, *J* = 8.3, 7.6 Hz, H-6), 7.15 (1H, dd, *J* = 8.0, 7.6 Hz, H-5), 3.84 (3H, s, CO_2CH_3), 3.66 (3H, s, N-CH_3).

^{13}C NMR: δ 165.79 ($\underline{C}OOCH_3$), 161.56 (CONH), 143.01 (s), 137.68 (s), 129.79 (d), 125.41 (s), 124.35 (d), 123.37 (s), 121.40 (d), 120.82 (d), 119.90 (s), 118.33 (d), 117.93 (s), 110.74 (d), 51.74 ($COO\underline{C}H_3$), 30.04 (N-CH_3).

Analysis calculated for $C_{36}H_{30}N_4O_6S_2 \cdot H_2O$ requires:

C, 62.1; H, 4.6; N, 8,1; S, 9.2%.

Found: C, 62.2; H, 4.6; N, 8.0; S, 9.2%.

A suspension of **(104)** (0.23 g, 0.34 mmol) in MeOH (40 mL) was treated with 3N KOH (15 mL) and stirred at 20°C for 90 minutes. The resulting solution was filtered, acidified, and the resulting precipitate collected and re-dissolved in CH_2Cl_2 (10 mL) containing MeOH (1 mL). H_2O_2 (0.20 mL of 30%) was added, and after 1 hour the solvents were removed under reduced pressure. The residue was triturated with MeOH to give 2,2'-dithiobis[*N*-(4'-carboxy)phenyl-1-methylindolyl-3-carboxamide] **(105)** [XX: R = 4-COOH] (100% yield); mp 221°C (dec).

^{1}H NMR ($(CD_3)_2SO$): δ 12.63 (1H; br, COOH), 9.78 (1H, s, CONH), 7.80 (1H, d, *J* = 8.0 Hz, H-4), 7.72 (2H, d,

J = 8.7 Hz, H-3',5'), 7.39 (1H, d, J = 8.4 Hz, H-7), 7.30 (2H, d, J = 8.7 Hz, H-2',6'), 7.28 (t, J = 8.4, 7.7 Hz, H-6), 7.16 (1H, t, J = 8.0, 7.7 Hz, H-5), 3.66 (3H, s, N-CH_3).

^{13}C NMR: δ 166.95 (COOH), 161.58 (CONH), 142.67 (s), 137.78 (s), 129.99 (d), 129.81 (s), 125.41 (s), 124.72 (s), 124.54 (d), 121.50 (d), 120.93 (d), 118.39 (d), 110.89 (d), 30.12 (N-CH_3).

Analysis calculated for $C_{34}H_{26}N_4O_6S_2\cdot0.5H_2O$ requires:

C, 61.9; H, 4.1; N, 8.5; S, 9.7%.

Found: C, 61.6; H, 4.2; N, 8.4; S, 9.9%.

Compounds 106 and 107 of Table 1

Similar treatment of 1-methyl-2-indolinethione [IV: R_1,R_2 = H, R_3 = CH_3] with the isocyanate [XIX: 3-COOMe] derived from monomethyl isophthalate gave 2,2'-dithiobis[N-(3'-carbomethoxy)phenyl-1-methylindolyl-3-carboxamide] (**106**) [XX: R = 3-COOMe] (57% yield); mp 193-195°C.

^{1}H NMR ((CD_3)$_2$SO): δ 9.67 (1H, s, CONH), 7.96 (1H, br s, H-2'), 7.79 (1H, d, J = 8.0 Hz, H-4), 7.56 (1H, d, J = 7.7 Hz, H-6'), 7.45 (1H, d, J = 8.2 Hz, H-7), 7.34 (1H, d, J = 8.3 Hz, H-4'), 7.28 (1H, dd, J = 8.3, 7.7 Hz, H-5'), 7.21 (1H, dd, J = 8.2, 7.7 Hz, H-6), 7.10 (1H, dd, J = 8.0, 7.7 Hz, H-5), 3.88 (3H, s, $COOCH_3$), 3.66 (3H, s, N-CH_3).

^{13}C NMR: δ 166.04 ($\underline{C}OOCH_3$), 161.48 (CONH), 138.89 (s), 137.63 (s), 129.77 (s), 129.54 (s), 128.62 (d), 125.21 (s), 124.39 (d), 123.51 (s), 121.28 (d), 120.83 (d), 119.50 (d), 118.31 (s), 110.64 (d), 51.99 ($COO\underline{C}H_3$), 30.02 (N-CH_3).

Analysis calculated for $C_{36}H_{30}N_4O_6S_2$ requires:

C, 63.7; H, 4.5; N, 8.3; S, 9.5%.

Found: C, 63.9; H, 4.6; N, 8.4; S, 9.6%.

Hydrolysis of the ester (**106**) as above, followed by re-oxidation with H_2O_2/MeOH, gave 2,2'-dithiobis[*N*-(3-carboxy)phenyl-1-methylindolyl-3-carboxamide] (**107**) [XX: R = 3-COOH] (97% yield); mp 219-220°C.
^{1}H NMR ($(CD_3)_2SO$): δ 12.68 (1H, br, COOH), 9.69 (1H, s, CONH), 7.98 (1H, br s, H-2'), 7.80 (1H, d, J = 8.0 Hz, H-4), 7.56 (1H, d, J = 7.7 Hz, H-6'), 7.43 (1H, d, J = 8.2 Hz, H-7), 7.36 (1H, d, J = 8.3, 7.7 Hz, H-4'), 7.24 (2H, m, H-5',6), 7.11 (1H, t, J = 8.0, 7.7 Hz, H-5), 3.66 (3H, s, $N-CH_3$).
^{13}C NMR: δ 167.10 (COOH), 161.53 (CONH), 138.77 (s), 137.62 (s), 130.92 (s), 129.47 (s), 128.44 (d), 125.18 (s), 124.45 (d), 123.75 (d), 123.31 (d), 121.32 (d), 120.81 (d), 119.91 (d), 118.51 (s), 110.67 (d), 30.01 ($N-CH_3$).
Analysis calculated for $C_{34}H_{26}N_4O_6S_2 \cdot 0.5H_2O$ requires: C, 61.9; H, 4.1; N, 8.5; S, 9.7%.
Found: C, 61.7; H, 4.3; N, 8.8; S, 9.7%.

<u>Compounds 108 & 109 of Table 1</u>

Similar treatment of 1-methyl-2-indolinethione [IV: R_1,R_2 = H, R_3 = CH_3] with the isocyanate [XIX: 2-COOMe] derived from monomethyl phthalate gave 2,2'-dithiobis[*N*-(2-carbomethoxy)phenyl-1-methylindolyl-3-carboxamide] (**108**) [XX: R = 2-COOMe] (61% yield); mp 179-181°C.
^{1}H NMR ($(CD_3)_2SO$): δ 10.82 (1H, s, CONH), 7.89 (2H, 2xd, J = 8.3, 8.0 Hz, H-3',6'), 7.74 (1H, d, J = 8.3 Hz, H-4), 7.32 (2H, m, H-7,4'), 7.20 (1H, dd, J = 8.1, 7.5 Hz, H-6), 7.12 (1H, dd, J = 8.3, 7.5 Hz, H-5), 6.97 (1H, m, H-5'), 3.84 (3H, s, $COOCH_3$), 3.68 (3H, s, $N-CH_3$).

Analysis calculated for $C_{36}H_{30}N_4O_6S_2 \cdot 0.5H_2O$ requires:
C, 62.9; H, 4.5; N, 8.2; S, 9.3%.
Found: C, 62.8; H, 4.5; N, 8.1; S, 9.3%.

Hydrolysis of the ester (108) as above, followed by re-oxidation with H_2O_2/MeOH, gave 2,2'-dithiobis[*N*-(2'-carboxy)phenyl-1-methylindolyl-3-carboxamide] (109) [XX: R = 2-COOH] (91% yield); mp 184-186°C.

^{1}H NMR ($(CD_3)_2SO$): δ 13.33 (1H, br, COOH), 11.31 (1H, s, CONH), 7.95 (1H, d, *J* = 8.1 Hz, H-6'), 7.90 (1H, d, *J* = 7.9 Hz, H-3'), 7.83 (1H, d, *J* = 8.3 Hz, H-4), 7.30 (2H, m, H-7,4'), 7.19 (1H, dd, *J* = 8.0, 7.5 Hz, H-6), 7.08 (1H, dd, *J* = 8.3, 7.5 Hz, H-5), 7.02 (1H, dd, *J* = 8.1, 7.8 Hz, H-5'), 3.67 (3H, s, N-CH_3).

^{13}C NMR: δ 169.16 (COOH), 160.71 (CONH), 140.55 (s), 137.78 (s), 133.31 (d), 130.50 (d), 129.30 (s), 125.01 (s), 124.50 (d), 121.79 (d), 121.47 (d), 121.05 (d), 120.28 (d), 118.21 (s), 115.91 (s), 110.68 (d), 29.93 (N-CH_3).

Analysis calculated for $C_{34}H_{26}N_4O_6S_2 \cdot 2H_2O$ requires:
C, 59.5; H, 4.4; N, 8.2; S, 9.3%.
Found: C, 59.3; H, 4.3; N, 8.3; S, 9.6%.

<u>Compound 110 of Table 1</u>

Similar treatment of 1-methyl-2-indolinethione [IV: R_1,R_2 = H, R_3 = CH_3] with the isocyanate derived from 4-(carbomethoxy)phenylacetic acid gave 2,2'-dithiobis[*N*-(4'-carbomethoxy)benzyl 1-methylindolyl-3-carboxamide] (110) [V: R_1 = H, R_2 = CONHCH_2Ph{4-COOMe}, R_3 = Me] (38% yield); mp 178-180°C.

^{1}H NMR ($(CD_3)_2SO$): δ 8.18 (1H, br, CONH), 7.88 (1H, d, *J* = 8.1 Hz, H-4), 7.82 (2H, d, *J* = 7.9 Hz, C-2',6'), 7.55 (1H, d, *J* = 8.3 Hz, H-7), 7.35 (1H, dd, *J* = 8.3, 7.7 Hz, H-6), 7.28 (2H, d, J = 7.9 Hz, C-3',5'), 7.20

(1H, dd, J = 8.1, 7.7 Hz, H-5), 4.06 (2H, d, J = 5.1 Hz, $CONHC\underline{H}_2$), 3.83 (3H, s, $COOCH_3$), 3.61 (3H, s, $N-CH_3$).
^{13}C NMR: δ 165.98 ($\underline{C}OOCH_3$), 163.17 (CONH), 145.10 (s), 137.61 (s), 129.06 (d), 129.00 (s), 127.85 (s), 126.95 (d), 125.37 (s), 124.31 (d), 121.22 (d), 121.09 (d), 117.89 (s), 110.78 (d), 51.89 ($COO\underline{C}H_3$), 41.90 (CH_2Ar), 29.94 ($N-CH_3$).
Analysis calculated for $C_{38}H_{34}N_4O_6S_2 \cdot 0.5H_2O$ requires:
C, 63.8; H, 4.9; N, 7.8; S, 8.9%.
Found: C, 63.7; H, 4.8; N, 7.8; S, 9.1%.

EXAMPLE I

Preparation of Compound 111 of Table 1 by the Method Outlined in Scheme 8.

A solution of 2-chloro-1-methylindole-3-carboxylic acid [XXI] (Marchetti L, Andreani A, Ann. Chim. (Rome) 1973;63:681) (0.95 g, 4.52 mmol) and $SOCl_2$ (0.99 mL, 13 mmol) in 1,2-dichloroethane (100 mL) containing DMF (1 drop) was heated under reflux under N_2 for 2 hours, then concentrated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL) and treated with a slurry of methyl 4-(aminomethyl)benzoate hydrochloride (Nair MG, Baugh CM, J. Org. Chem. 1973;38:2185) (1.00 g, 4.98 mmol) and Et_3N (1.58 mL, 11 mmol) in CH_2Cl_2 (50 mL). After vigorous stirring at 20°C for 24 hours, the mixture was washed with water and the organic portion worked up to give N-(4'-carbomethoxy)-benzyl 2-chloro-1-methylindole-3-carboxamide [XXII: R_6 = H, R_7 = $CH_2Ph\{4\text{-}COOMe\}$] (1.40 g, 86%) which crystallized from aqueous acetone; mp 108-110°C. ^1H NMR ($(CD_3)_2SO$): δ 8.38 (1H, t, J = 5.8 Hz, $CON\underline{H}CH_2$), 7.95 (2H, d, J = 7.9 Hz, H-2',6'), 7.91 (1H, d, J = 7.8 Hz, H-4), 7.56 (1H, d, J = 7.9 Hz, H-7), 7.52

(2H, d, J = 7.9 Hz, H-3',5'), 7.29 (1H, dd, J = 7.9, 7.1 Hz, H-6), 7.19 (1H, dd, J = 7.8, 7.1 Hz, H-5), 4.60 (2H, d, J = 5.8 Hz, CONHC$\underline{H}_2$), 3.84 (3H, s, $COOCH_3$), 3.79 (3H, s, N-CH_3).

^{13}C NMR: δ 166.09 ($\underline{C}OOCH_3$), 162.77 (CONH), 145.65 (s), 135.00 (s), 129.18 (d), 129.14 (d), 127.94 (s), 127.34 (d), 127.25 (d), 126.34 (s), 124.77 (s), 122.57 (d), 121.19 (d), 119.97 (d), 110.21 (s), 107.11 (d), 51.95 (COO$\underline{C}H_3$), 42.15 (CH_2), 29.97 (N-CH_3).

Analysis calculated for $C_{19}H_{17}ClN_2O_3$ requires:

C, 64.0; H, 4.8; N, 7.9; Cl, 9.9%.

Found: C, 64.0; H, 4.8; N, 7.6; Cl, 9.8%.

A solution of the above carboxamide (1.00 g, 2.80 mmol) in DMA (10 mL) was added under N_2 to a stirred suspension of MeSLi (1.06 g, 19 mmol) in DMA (25 mL). After warming at 80°C for 6 hours, the mixture was acidified with 3N HCl, extracted with CH_2Cl_2, and worked up to give a yellow oil. Traces of DMA were removed under high vacuum, and the residue was dissolved in MeOH (20 mL) and treated dropwise with H_2O_2 (0.60 mL of 30% solution). After chilling at -30°C overnight, the precipitate was filtered off, washed well with MeOH, and dried to give 2,2'-dithiobis[*N*-(4'-carboxy)benzyl 1-methylindol-3-carboxamide] (**111**) [V: R_1 = H, R_2 = CONHCH$_2$Ph{4-COOH}, R_3 = Me] (0.68 g, 72%); mp 178-180°C.

^1H NMR ($(CD_3)_2SO$): δ 12.86 (1H, br, COOH), 8.13 (1H, t, J = 5.8 Hz, CON$\underline{H}CH_2$), 7.92-7.80 (3H, m, H-4,2',6'), 7.56 (1H, d, J = 8.3 Hz, H-7), 7.37 (1H, t, J = 8.3, 7.8 Hz, H-6), 7.27 (2H, d, J = 8.3 Hz, H-3',5'), 7.20 (1H, dd, J = 8.1, 7.8 Hz, H-5), 4.02 (2H, d, J = 5.8 Hz, CONHC$\underline{H}_2$), 3.62 (3H, s, N-CH_3).

^{13}C NMR: δ 167.08 (COOH), 163.08 (CONH), 144.51 (s), 137.64 (s), 130.35 (s), 129.25 (d), 129.04 (s), 126.85 (d), 125.25 (s), 124.44 (d), 121.23 (d), 121.10 (d), 118.33 (s), 110.87 (d), 41.92 (CH_2), 29.94 (N-CH_3).
Analysis calculated for $C_{36}H_{30}N_4O_6S2 \cdot 1.5H_2O$ requires:
C, 61.3; H, 4.7; N, 7.9; S, 9.1%.
Found: C, 61.1; H, 4.8; N, 8.3; S, 9.0%.

Compound 112 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and glycine methyl ester hydrochloride gave *N*-carbomethoxymethyl 2-chloro-1-methylindole-3-carboxamide [XXII: R_6 = H, R_7 = CH_2COOMe] (78% yield); mp ($CHCl_3$/light petroleum) 102.5-104°C.
^1H NMR ($CDCl_3$): δ 8.26 (1H, d, *J* = 8.1 Hz, H-4), 7.30-7.23 (3H, m, H-5,6,7), 6.96 (1H, br, CONH), 4.32 (2H, d, *J* = 5.0 Hz, $C\underline{H}_2NHCO$), 3.81 (3H, s, $COOCH_3$), 3.75 (3H, s, N-CH_3).
^{13}C NMR: δ 170.91 ($\underline{C}OOCH_3$), 163.48 (CONH), 135.45 (s), 126.90 (s), 125.93 (s), 123.24 (d), 122.25 (d), 121.30 (d), 109.26 (d), 106.32 (s), 52.41 ($COO\underline{C}H_3$), 41.38 ($C\underline{H}_2COOMe$), 30.11 (N-CH_3).
Analysis calculated for $C_{13}H_{13}ClN_2O_3$ requires:
C, 55.6; H, 4.7; N, 10.0%.
Found: C, 55.3; H, 4.8; N, 10.2%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-carboxymethyl 1-methylindolyl-3-carboxamide] (112) [V: R_1 = H, R_2 = $CONHCH_2COOH$, R_3 = Me] (56% yield); mp 197°C (dec).
^1H NMR ($(CD_3)_2SO$): δ 7.98 (1H, d, *J* = 8.1 Hz, H-4), 7.59 (1H, br, CONH), 7.55 (1H, d, *J* = 8.4 Hz, H-7), 7.35 (1H, dd, *J* = 8.4, 7.5 Hz, H-6), 7.20 (1H, dd,

J = 8.1, 7.5 Hz, H-5), 3.68 (3H, s, N-CH_3), 3.20 (2H, d, J = 5.2 Hz, $C\underline{H}_2$COOH).
^{13}C NMR: δ 171.02 (COOH), 162.57 (CONH), 137.60 (s), 125.36 (s), 124.30 (d), 121.27 (d), 121.11 (d), 117.69 (s), 110.65 (d), 40.35 (CH_2), 29.87 (N-CH_3).
Analysis calculated for $C_{24}H_{22}N_4O_6S_2 \cdot H_2O$ requires:
C, 52.9; H, 4.4; N, 10.3; S, 11.8%.
Found: C, 52.5; H, 4.5; N, 10.0; S, 11.2%.

Compound 113 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and N-methylaniline gave *N*-methyl-*N*-phenyl 2-chloro-1-methylindole-3-carboxamide [XXII: R_6 = Me; R_7 = Ph] (67% yield); mp (Me_2CO/water) 163°C.
^{1}H NMR ($(CD_3)_2SO$): δ 7.47 (1H, d, J = 7.6 Hz, H-4), 7.41 (1H, d, J = 8.3 Hz, H-7), 7.22-7.00 (7H, m, ArH), 3.63 (3H, s, N-CH_3), 3.42 (3H, s, N-CH_3).
^{13}C NMR: δ 164. 33 (CONMePh), 143.88 (s), 134.69 (s), 128.50 (d), 125.90 (d), 125.70 (d), 124.86 (s), 124.21 (s), 122.24 (d), 120.71 (d), 118.94 (d), 110.06 (d), 108.80(s), 37.40 (N-CH_3), 29.77 (N-CH_3).
Analysis calculated for $C_{17}H_{15}ClN_2O$ requires:
C, 68.3; H, 5.1; N, 9.4; Cl, 11.9%.
Found: C, 68.4; H, 5.1; N, 9.3; Cl, 12.1%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-methyl-*N*-phenyl-1-methylindolyl-3-carboxamide] (**113**) [V: R_1 = H, R_2 = CON(Me)Ph, R_3 = Me] (53% yield), mp 158-163°C.
^{1}H NMR ($(CD_3)_2SO$): δ 7.80 (1H, d, J = 7.5 Hz, H-4), 7.57 (1H, d, J = 7.8 Hz, H-7), 7.33-6.99 (7H, m, ArH), 3.86 (3H, s, N-CH_3), 3.33 (3H, s, N-CH_3).
^{13}C NMR: δ 164.14 (CONMePh), 137.59 (s), 129.94 (s), 124.21 (s), 123.73 (s), 123.24 (d), 122.34 (d), 120.25

(d), 119.56 (d), 118.79 (d), 115.43 (s), 110.27 (d), 39.68 ($N-CH_3$), 30.99 ($N-CH_3$).

Analysis calculated for $C_{34}H_{31}N_4S_2O_2$ requires: $[M + H]^+$ 591.3447.

Found: $[M + H]^+$ 591.3441 (FAB mass spectrum).

Analysis calculated for $C_{34}H_{30}N_4S_2O_2$ requires: C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 69.2; H, 5.2; N, 9.6; S, 10.6%.

Compound 114 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and 3-aminopropane-1,2-diol gave *N*-(2,3-dihydroxypropyl)-2-chloro-1-methylindole-3-carboxamide [XXII: R_6 = H;, R_7 = $CH_2CH(OH)CH_2OH$] (46%) as an oil.

^1H NMR ($(CD_3)_2SO/D_2O$): δ 7.94 (1H, d, *J* = 7.0 Hz, H-4), 7.53 (1H, d, *J* = 7.2 Hz, H-7), 7.38-7.19 (2H, m, H-5,6), 3.78 (3H, s, $N-CH_3$), 3.68-3.26 (5H, m, $C\underline{H}_2C\underline{H}OHC\underline{H}_2OH$).

^{13}C NMR: δ 162.72 (CONH), 134.94 (s), 125.94 (s), 124.79 (s), 122.52 (d), 121.15 (d), 120.05 (d), 110.17 (d), 107.09 (d), 70.17 (CHOH), 63.90 (CH_2OH), 42.34 ($CONH\underline{C}H_2$), 29.97 ($N-CH_3$).

Analysis calculated for $C_{13}H_{15}ClN_2O_3$ requires: M^+ 284.0742, 282.0771.

Found: M^+ 284.0744, 282.0763 (mass spectrum).

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-(2,3-dihydroxypropyl)-1-methyl-indolyl-3-carboxamide] (**114**) [V: R_1 = H, R_2 = $CONHCH_2CH(OH)CH_2OH$, R_3 = Me] (71% yield) as a yellow foam; mp 198°C (dec).

^1H NMR ($(CD_3)_2SO/D_2O$): δ 7.89 (1H, d, *J* = 8.1 Hz, H-4), 7.56 (1H, d, *J* = 8.4 Hz, H-7), 7.42 (1H, dd, *J* = 8.4, 7.3 Hz, H-6), 7.27 (1H, dd, *J* = 8.1, 7.3 Hz,

H-5), 3.75 (3H, s, N-CH_3), 3.40-3.20 (5H, m, $C\underline{H}_2C\underline{H}OHC\underline{H}_2OH$).
^{13}C NMR: δ 162.61 (CONH), 137.70 (s), 125.21 (s), 124.40 (d), 121.34 (d), 121.27 (d), 120.81 (s), 117.85 (s), 110.88 (d), 70.17 (CHOH), 63.75 (CH_2OH), 41.96 ($CONH\underline{C}H_2$), 29.95 (N-CH_3).
Analysis calculated for $C_{26}H_{30}N_4O_6S_2$ requires:
C, 55.9; H, 5.4; N, 10.0; S, 11.5%.
Found: C, 55.4; H, 5.4; N, 9.7; S, 11.5%.

Compound 115 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and *N,N*-dimethylethylenediamine, followed by extraction into 3N HCl, neutralization with aqueous NH_3 and extraction with EtOAc gave *N,N*-dimethylaminoethyl-2-chloro-1-methylindole-3-carboxamide [XXII: R_6 = H, R_7 = $CH_2CH_2NMe_2$] as an oil (74% yield), which eventually solidified; mp 63°C.
^1H NMR ($CDCl_3$): δ 8.20 (1H, dd, *J* = 8.1, 1.7 Hz, H-4), 7.26-7.20 (3H, m, H-5,6,7), 7.01 (1H, br, CONH), 3.69 (3H, s, N-CH_3), 3.58 (2H, dt, *J* = 6.1, 5.1 Hz, $CONHC\underline{H}_2$), 2.55 (2H, t, *J* = 6.1 Hz, $C\underline{H}_2N(CH_3)_2$, 2.30 (6H, s, $N(CH_3)$)).
^{13}C NMR: δ 163.62 (CONH), 135.31 (s), 126.43 (s), 125.79 (s), 122.90 (d), 121.83 (d), 121.06 (d), 109.17 (d), 107.07 (s), 57.84 ($CONH\underline{C}H_2$), 45.14 ($N(CH_3)_2$), 36.80 $\underline{C}H_2N(CH_3)_2$), 29.96 (N-$CH_3$).
Analysis calculated for $C_{14}H_{18}ClN_3O$ requires:
M^+ 281.1109, 279.1138.
Found: M^+ 281.1106, 279.1118 (mass spectrum).

Following treatment of this with MeSLi as above, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic portion was extracted with 3N HCl,

and the extract was neutralized with aqueous NH_3, extracted with CH_2Cl_2, and worked up to give an oil which was dissolved in MeOH and allowed to stand at 20°C for 48 hours. The product was adsorbed directly onto silica and chromatographed. Elution with MeOH/EtOAc (1:19) containing a trace of concentrated $NH4_oH$ gave 2,2'-dithiobis[*N*-(*N*,*N*-dimethylaminoethyl) 1-methylindolyl-3-carboxamide] (**115**) [V: R_1 = H, R_2 = $CONHCH_2CH_2NMe_2$, R_3 = Me] (54% yield); mp (CH_2Cl_2/light petroleum) 163.5-165°C.
^{1}H NMR ($CDCl_3$): δ 8.24 (1H, d, *J* = 8.1 Hz, H-7), 7.36 (1H, dd, *J* = 8.2, 7.8 Hz, H-6), 7.30 (1H, d, *J* = 8.2 Hz, H-7), 7.25 (1H, dd, *J* = 8.1, 7.8 Hz, H-5), 7.10 (1H, br, CONH), 3.60 (3H, s, N-CH_3), 2.99 (2H, dt, *J* = 6.3, 5.5 Hz, CONHC$\underline{H}_2$), 2.26 (2H, t, *J* = 6.3 Hz, C$\underline{H}_2$N(CH_3)$_2$), 2.21 (6H, s, N(CH_3)$_2$).
^{13}C NMR: δ 163.71 (CONH), 138.27 (s), 126.64 (s), 125.20 (d), 122.70 (d), 122.11 (d), 118.46 (s), 110.08 (d), 57.72 (CONH$\underline{C}H_2$), 45.19 (N(CH_3)$_2$), 36.81 ($\underline{C}H_2$N(CH_3)$_2$), 30.15 (N-CH_3).
Analysis calculated for $C_{28}H_{36}N_6O_2S_2$ requires:
C, 60.8; H, 6.6; N, 15.2; S, 11.6%.
Found: C, 60.7; H, 6.8; N, 14.9; S, 11.4%.

<u>Compound **116** of Table 1</u>

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and 4-aminopyridine gave *N*-(4-pyridyl)-2-chloro-1-methylindole-3-carboxamide [XXII: R_6 = H, R_7 = 4-pyridyl] (61% yield); mp ($CHCl_3$/light petroleum) 220-223°C.
^{1}H NMR ((CD_3)$_2$SO): δ 10.28 (1H, br, CONH), 8.47 (2H, d, *J* = 6.1 Hz, H-2',6'), 7.82 (1H, d, *J* = 7.5 Hz, H-4), 7.72 (2H, d, *J* = 6.1 Hz, H-3',5'), 7.63 (1H, d, *J* = 8.0 Hz, H-7), 7.33 (1H, dd, *J* = 8.0, 7.6 Hz, H-6),

7.25 (1H, dd, J = 7.6, 7.5 Hz, H-5), 3.84 (3H, s, N-CH_3).
^{13}C NMR: δ 162.03 (CONH), 150.16 (d), 145.81 (s), 134.98 (s), 127.50 (s), 124.49 (s), 122.81 (d), 121.54 (d), 119.59 (d), 113.50 (d), 110.47 (d), 107.60 (s), 30.11 (N-CH_3).
Analysis calculated for $C_{15}H_{12}ClN_3O$ requires:
C, 63.1; H, 4.2; N, 14.7%.
Found: C, 62.8; H, 3.9; N, 14.6%.

Reaction of this with MeSLi as above gave 2,2'-dithiobis[*N*-(4-pyridyl)-1-methylindolyl-3-carboxamide] (**116**) [V: R_1 = H, R_2 = CONH-4-pyridyl, R_3 = Me] (53% yield); mp 226-229°C (dec).
^1H NMR ($(CD_3)_2SO$): δ 14.46 (1H, s, CONH), 8.51 (2H, d, J = 7.0 Hz, H-2',6'), 8.13 (2H, d, J = 7.0 Hz, H-3',5'), 8.05 (1H, d, J = 7.9 Hz, H-4), 7.16 (1H, d, J = 8.1 Hz, H-7), 7.00 (2H, m, H-5,6), 3.68 (3H, s, N-CH_3).
^{13}C NMR: δ 165.13 (s), 164.33 (CONH), 153.80 (s), 141.35 (d), 137.26 (s), 128.35 (s), 120.30 (d), 119.97 (d), 118.52 (d), 112.83 (d), 107.66 (d), 104.06 (s), 29.37 (N-CH_3).
Analysis calculated for $C_{30}H_{24}N_6O_2S_2$ requires:
C, 62.8; H, 4.4; N, 14.6; S, 11.2%.
Found: C, 62.4; H, 4.9; N, 14.5; S, 11.4%.

<u>Compound 117 of Table 1</u>

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and 3-aminopyridine gave *N*-(3-pyridyl)-2-chloro-1-methylindole-3-carboxamide [XXII: R_7 = H, R_8 = 3-pyridyl] (86% yield); mp (EtOAc/light petroleum) 175-177°C.
^1H NMR ($(CD_3)_2SO$): δ 10.13 (1H, s, CONH), 8.90 (1H, d, J = 2.4 Hz, H-2'), 8.30 (1H, dd, J = 4.7, 1.4 Hz,

H-6'), 8.18 (1H, ddd, J = 4.5, 2.4, 1.4 Hz, H-4'), 7.84 (1H, d, J = 7.9 Hz, H-4), 7.63 (1H, d, J = 8.2 Hz, H-7), 7.40 (1H, dd, J = 4.7, 4.5 Hz, H-5'), 7.32 (1H, dd, J = 8.2, 7.7 Hz, H-6), 7.25 (1H, dd, J = 7.9, 7.7 Hz, H-5), 3.84 (3H, s, N-CH_3).

^{13}C NMR: δ 161.71 (CONH), 144.11 (d), 141.38 (d), 135.85 (s), 134.98 (s), 127.15 (s), 126.62 (d), 124.51 (s), 123.46 (d), 122.74 (d), 121.43 (d), 119.70 (d), 110.43 (d), 107.69 (s), 30.09 (N-CH_3).

Analysis calculated for $C_{15}H_{12}ClN_3O$ requires:

C, 63.1; H, 4.1; N, 14.3; Cl, 13.6%.

Found: C, 63.2; H, 4.2; N, 14.9; Cl, 12.4%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-(3-pyridyl) 1-methylindolyl-3-carboxamide] (**117**) [V: R_1 = H, R_2 = CONH-3-pyridyl, R_3 = Me] (71% yield); mp 257-260°C.

^1H NMR (($(CD_3)_2SO$): δ 13.82 (1H, s, CONH), 9.53 (1H, d, J = 1.6 Hz, H-2'), 8.44 (2H, m, H-4',6'), 8.05 (1H, d, J = 8.0 Hz, H-4), 7.91 (1H, dd, J = 4.6, 4.5 Hz, H-5'), 7.14 (1H, d, J = 8.1 Hz, H-7), 6.96 (2H, m, H-5',6'), 3.67 (3H, s, N-CH_3).

^{13}C NMR: δ 164.76 (CONH), 162.70 (s), 140.01 (s), 136.97 (s), 134.17 (d), 132.51 (d), 131.06 (d), 128.44 (s), 127.08 (d), 119.90 (d), 119.45 (d), 118.39 (d), 107.50 (d), 103.89 (s), 29.25. (N-CH_3).

Analysis calculated for $C_{30}H_{24}N_6O_2S_2$ requires:

C, 63.8; H, 4.3; N, 14.9; S, 11.4%.

Found: C, 63.5; H, 4.9; N, 14.8; S, 11.1%.

<u>Compound 118 of Table 1</u>

Treatment of 2-chloro-1-methylindole-3-carboxamide [XXII: R_7 = R_8 = H] (Andreani A, Rambaldi M, <u>J. Het. Chem.</u> 1988;25:1519-1523) with MeSLi as above gave 2,2'-dithiobis[1-methylindolyl-3-carboxamide] (**118**)

[V: R_1 = H, R_2 = $CONH_2$, R_3 = Me] (71% yield); mp 186-188°C.

^1H NMR ($(CD_3)_2SO$): δ 7.99 (1H, d, *J* = 7.9 Hz, H-4), 7.52 (1H, d, *J* = 8.3 Hz, H-7), 7.33 (1H, dd, *J* = 8.3, 7.2 Hz, H-6), 7.25-7.11 (3H, m, H-5 and $CONH_2$), 3.48 (3H, s, N-CH_3).

^{13}C NMR: δ 164.76 ($CONH_2$), 137.56 (s), 129.35 (s), 125.51 (s), 124.37 (d), 121.58 (d), 121.23 (d), 117.77 (s), 110.74 (d), 29.82 (N-CH_3).

Analysis calculated for $C_{20}H_{18}N_4O_2S_2 \cdot 0.5H_2O$ requires:
C, 57.3; H, 4.6; N, 13.4; S, 15.3%.
Found: C, 57.7; H, 4.5; N, 13.5; S, 15.4%.

Compound 119 of Table 1

Treatment of *N,N*-dimethyl 2-chloro-1-methylindole-3-carboxamide [XXII: R_7 = R_8 = Me] (Bergman J, Carlsson R, Sjöberg B, J. Het. Chem. 1977;14:1123-1134) with MeSLi as above gave 2,2'-dithiobis[*N,N*-dimethyl-1-methylindolyl-3-carboxamide] (119) [V: R_1 = H, R_2 = $CONMe_2$, R_3 = Me]. Chromatography on silica gel, eluting with EtOAc, followed by crystallization from EtOAc/light petroleum gave pure material (54% yield); mp 96-102°C.

^1H NMR ($CDCl_3$): δ 7.43 (1H, d, *J* = 8.0 Hz, H-4), 7.31 (2H, m, H-6,7), 7.15 (1H, m, H-5), 3.64 (3H, s, N-CH_3), 2.91, 2.62 (2x3H, 2xbr, $N(CH_3)_2$).

^{13}C NMR: δ 165.89 ($CONMe_2$), 138.06 (s), 128.51 (s), 125.04 (s), 124.47 (d), 121.15 (d), 120.59 (d), 120.19 (s), 110.19 (d), 38.65 ($N(CH_3)_2$), 34.84 ($N(CH_3)_2$), 30.23 (N-CH_3).

Analysis calculated for $C_{24}H_{26}N_4O_2S_2 \cdot 0.5H_2O$ requires:
C, 60.6; H, 5.7; N, 11.7%.
Found: C, 60.3; H, 5.8; N, 11.2%.

Analysis calculated for $C_{24}H_{27}N_4S_2O_2$ requires:
[M + H]$^+$ 467.1575.
Found: [M + H]$^+$ 467.1559 (FAB mass spectrum).

Compound 120 of Table 1

A mixture of 2-chloroindole-3-carboxaldehyde (7.0 g, 36 mmol) was reacted with a slight excess of hydroxylamine hydrochloride and pyridine in refluxing EtOH for 1 hour, to give the crude oxime (Latrell R, Bartmann W, Musif J, Granzer E, German Patent 2,707,268, 31 Aug 1978, Chem. Abstr. 1978;89:179858y). A solution of this in Ac_2O (100 mL) was heated under reflux for 1 hour, cooled, and stirred with water (700 mL). The precipitated solid was collected, washed with water, and crystallized from aqueous MeOH to give 2-chloro-1*H*-indole-3-carbonitrile (3.7 g, 58%); mp 177-180°C.
^{1}H NMR ($(CD_3)_2SO$): δ 13.23 (1H, s, NH), 7.60 (1H, d, J = 7.5 Hz, ArH), 7.50 (1H, d, J = 7.9 Hz, ArH), 7.34 (1H, t, J = 7.5 H, ArH), 7.29 (1H, t, J = 7.3 Hz, ArH).
^{13}C NMR: δ 134.0, 131.5, 126.2, 114.1 (C), 123.8, 122.3, 117.9, 112.3 (CH), 83.8 (CN).
Analysis calculated for $C_9H_5ClN_2$ requires:
C, 61.2; H, 2.9; N, 15.9%.
Found: C, 61.2; H, 2.7; N, 15.9%.

A solution of the above nitrile (2.5 g, 14 mmol) in Me_2CO was treated with a slight excess of MeI and K_2CO_3 under reflux for 1 hour. Crystallization of the crude product from hexane gave 2-chloro-1-methylindole-3-carbonitrile (1.88 g, 70%); mp 112-114°C.
^{1}H NMR ($CDCl_3$): δ 7.61-7.55 (1H, m, ArH), 7.34-7.21 (3H, m, ArH), 3.74 (3H, s, CH_3).
^{13}C NMR: δ 135.0, 133.4, 126.0, 114.1 (C), 123.9, 122.7, 118.8, 110.1 (CH), 85.2 (CN).

Analysis calculated for $C_{10}H_7ClN_2$ requires:
C, 63.0; H, 3.7; N, 14.7%.
Found: C, 63.0; H, 3.6; N, 14.7%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis(2-chloro-1-methylindole-3-carbonitrile) (**120**) [V: R_1 = H, R_2 = CN, R_3 = Me] (53% yield); mp 205-207°C.
^{1}H NMR ($(CD_3)_2SO$): δ 7.69 (1H, d, J = 8.3 Hz, H-4), 7.51 (1H, d, J = 8.0 Hz, H-7), 7.42 (1H, dd, J = 8.0, 7.3 Hz, H-6), 7.28 (1H, dd, J = 8.3, 7.3 Hz, H-5), 3.82 (3H, s, N-CH_3).
Analysis calculated for $C_{20}H_{14}N_4S_2$ requires:
C, 64.2; H, 3.8; N, 15.0; S, 17.1%.
Found: C, 64.2; H, 3.8; N, 15.1; S, 17.7%.

Compound 121 of Table 1

3-Acetyl-2-chloro-1-methylindole was prepared by the reported method (Coppola GM, Hardtmann GE, J. Het. Chem. 1977;14:117-1118). This was reacted with MeSLi as above gave 3-acetyl-1-methyl-2-indolinethione [XV: R_5 = Me] (66% yield); mp 180°C.
^{1}H NMR ($(CD_3)_2SO$): δ 15.60 (1H, br, SH), 7.64 (1H, d, J = 6.5 Hz, H-4), 7.39 (1H, d, J = 7.6 Hz, H-7), 7.32 (1H, dd, J = 7.6, 7.3 Hz, H-6), 7.24 (1H, dd, J = 7.3, 6.5 Hz, H-5), 3.65 (3H, s, N-CH_3), 2.66 (3H, s, $COCH_3$).
^{13}C NMR: δ 178.29 ($COCH_3$), 140.56 (s), 125.21 (d), 124.67 (s), 123.27 (d), 120.60 (d), 111.31 (s), 109.99 (d), 29.31 (N-CH_3), 22.44 ($COCH_3$).
Analysis calculated for $C_9H_5ClN_2$ requires:
C, 61.2; H, 2.9; N, 15.9%.
Found: C, 61.2; H, 2.7; N, 15.9%.

A solution of the above thione (0.10 g, 0.49 mmol) in MeOH/EtOAc (1:9) (10 mL) was stirred vigorously with 30% H_2O_2 (0.20 mL) for 4 hours. The solution was

concentrated to a volume of 0.5 mL, and the orange precipitate was filtered off and washed well with MeOH to give 2,2'-dithiobis(3-acetyl-1-methylindole) (**121**) [V: R_1 = H, R_2 = COMe, R_3 = Me] (100% yield); mp 178.5-179.5°C.

^{1}H NMR ($(CD_3)_2SO$): δ 8.14 (1H, d, J = 8.1 Hz, H-4), 7.62 (1H, d, J = 8.3 Hz, H-7), 7.39 (1H, dd, J = 8.3, 7.3 Hz, H-6), 7.27 (1H, dd, J = 8.1, 7.3 Hz, H-5), 3.75 (3H, s, N-CH_3), 2.00 (3H, s, $COCH_3$).

^{13}C NMR: δ 192.56 ($COCH_3$), 137.65 (s), 133.73 (s), 125.41 (s), 124.79 (d), 122.73 (d), 121.95 (d), 121.43 (s), 110.92 (d), 30.34 ($COCH_3$), 29.43 (N-CH_3).

Analysis calculated for $C_{22}H_{20}N_2O_2S_2\cdot0.5H_2O$ requires:
C, 63.3; H, 5.1; N, 6.7%.
Found: C, 63.7; H, 4.7; N, 6.8%.

Compound 122 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and 2-aminopyridine gave N-(2'-pyridyl)-2-chloro-1-methylindole-3-carboxamide [XXII: R_6 = H, R_7 = 2-pyridyl] (42% yield); mp (light petroleum) 123°C.

^{1}H NMR ($CDCl_3$): δ 8.85 (1H, s, CONH), 8.41 (1H, d, J = 8.4 Hz, H-4), 8.30 (2H, m), 7.72 (1H, m), 7.28 (3H, m), 7.02 (1H, dd, J = 7.2, 4.9 Hz), 3.74 (3H, s, N-CH_3).

^{13}C NMR: δ 161.58 (CONH), 151.85 (s), 147.92 (d), 138.27 (d), 135.46 (s), 127.22 (s), 125.84 (s), 123.45 (d), 122.48 (d), 121.16 (d), 119.47 (d), 114.25 (d), 109.44 (d), 106.59 (s), 30.21 (N-CH_3).

Analysis calculated for $C_{15}H_{12}ClN_3O$ requires:
C, 63.1; H, 4.2; N, 14.7%.
Found: C, 62.9; H, 4.2; N, 14.4%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-(2'-pyridyl)-1-methylindole-3-carboxamide] (122) [V: R_1 = H, R_2 = CONH-2-pyridyl, R_3 = Me] (68% yield); mp 270-272°C (dec).
^{1}H NMR ($(CD_3)_2SO$): δ 14.93 (1H, br, CONH), 8.32 (1H, d, *J* = 6.0 Hz), 8.25 (1H, dd, *J* = 8.3, 7.7 Hz), 8.02 (1H, dd, *J* = 7.4, 3.7 Hz), 7.57 (1H, d, *J* = 8.7 Hz), 7.35 (1H, t, *J* = 6.6 Hz), 7.21 (1H, dd, *J* = 5.1, 3.0 Hz), 7.04 (2H, m), 3.69 (3H, s, N-CH_3).
^{13}C NMR: δ 166.48 (s), 165.41 (CONH), 149.16 (s), 145.34 (d), 137.66 (s), 137.49 (s), 127.89 (s), 120.66 (d), 120.44 (d), 118.32 (d), 117.55 (d), 115.32 (d), 107.96 (d), 102.69 (s), 29.40 (N-CH_3).
Analysis calculated for $C_{30}H_{24}N_6O_2S_2 \cdot 0.25H_2O$ requires:
C, 63.3; H, 4.3; N, 14.8; S, 11.3%.
Found: C, 63.2; H, 4.5; N, 14.8; S, 11.7%.

<u>Compound 123 of Table 1</u>

Similar treatment of 1-methyl-2-indolinethione [IV: R_1,R_2 = H, R_3 = CH_3] with the acyl azide derived from 2-furoic acid gave 3-(2-furoyl)-1-methyl-2-indolinethione [IV: R_1 = H, R_2 = CO(2-furyl); R_3 = Me] (85% yield); mp 113.5°C.
^{1}H NMR ($(CD_3)_2SO$): δ 15.90 (1H, br, SH), 8.28 (1H, d, *J* = 1.6 Hz, H-5'), 7.97 (1H, d, *J* = 8.0 Hz, H-4), 7.56 (1H, d, *J* = 3.6 Hz, H-3'), 7.46 (1H, d, *J* = 8.0 Hz, H-7), 7.37 (1H, dd, *J* = 8.0, 7.4 Hz, H-6), 7.21 (1H, dd, *J* = 8.0, 7.4 Hz, H-5), 6.94 (1H, dd, *J* = 3.6, 1.6 Hz, H-4'), 3.72 (3H, s, N-CH_3).
^{13}C NMR: δ 180.09 (CS), 160.65 (CO), 147.95 (d), 147.27 (s), 140.92 (s), 126.05 (d), 123.26 (s), 123.12 (d), 121.04 (d), 119.19 (d), 113.22 (d), 110.11 (d), 109.64 (s), 29.79 (N-CH_3).

Analysis calculated for $C_{14}H_{11}NO_2S$ requires:
C, 65.3; H, 4.4; N, 5.7; S, 12.7%.
Found: C, 65.4; H, 4,3; N, 5.4; S, 12.5%.

Reaction of the above compound with I_2 as described above gave 2,2'-dithiobis[3-(2-furoyl)-1-methylindole] (**123**) [V: R_1 = H; R_2 = CO(2-furyl); R_3 = Me] (85% yield); mp 175-176.5°C.

^{1}H NMR ($CDCl_3$): δ 7.47 (1H, d, J = 8.1 Hz, H-4), 7.33 (1H, dd, J = 1.6, 0.7 Hz, H-5'), 7.23 (1H, dd, J = 8.1, 7.8 Hz, H-6), 7.21 (1H, d, J = 8.1 Hz, H-7), 7.09 (1H, dd, J = 8.1, 7.9 Hz, H-5), 6.63 (1H, dd, J = 3.6, 0.7 Hz, H-3'), 6.23 (1H, dd, J = 3.6, 1.6 Hz, H-4'), 3.73 (3H, s, NCH_3).

^{13}C NMR: δ 177.09 (CO), 152.55 (s), 145.91 (d), 138.18, 131.32, 125.80 (3xs), 124.72 (d), 123.60 (s), 121.73, 121.12, 119.16, 111.91, 110.06 (5xd), 30.54 (NCH_3).

Analysis calculated for $C_{28}H_{20}N_2O_4S_2 \cdot 0.5H_2O$ requires:
Found: C, 64.4; H, 4.1; N, 5.4; S, 12.3%.
C, 64.7; H, 4.1; N, 5.6; S, 12.4%.

<u>Compound 124 of Table 1</u>

Similar treatment of 1-methyl-2-indolinethione [IV: R_1,R_2 = H, R_3 = CH_3] with the isocyanate derived from thiophene-2-carboxylic acid gave 2,2'-dithiobis[*N*-(2-thienyl)-1-methylindole-3-carboxamide] (**124**) [V: R_1 = H, R_2 = CONHfuryl, R_3 = Me] (21% yield; mp 183°C (dec).

^{1}H NMR ($(CD_3)_2SO$): δ 11.26 (1H, s, CONH), 7.93 (1H, d, *J* = 8.0 Hz, H-4), 7.62 (1H, d, *J* = 8.3 Hz, H-7), 7.34 (1H, dd, *J* = 8.3, 7.4 Hz, H-6), 7.24 (1H, dd, *J* = 8.0, 7.4 Hz, H-5), 7.05 (1H, dd, *J* = 5.3, 3.6 Hz, H-4'), 6.94 (1H, d, *J* = 5.3 Hz, H-5'), 6.41 (1H, d, *J* = 3.6 Hz, H-3'), 3.95 (3H, s, NCH_3).

^{13}C NMR: δ 160.10 (CONH), 139.86 (s), 137.81 (s), 136.86 (s), 125.19 (s), 123.96 (d), 123.69 (d), 121.28 (d), 120.54 (d), 116.85 (d), 114.73 (s), 111.20 (d), 110.77 (d), 30.54 ($N-CH_3$).

Analysis calculated for $C_{28}H_{22}N_4O_2S_4 \cdot H_2O$ requires:
C, 57.6; H, 4.0; N, 9.6%.
Found: C, 57.6; H, 4.1; N, 10.0%.

EXAMPLE J

Preparation of Compound 125 of Table 1 by the Method Outlined in Scheme 9

Reaction of 3-chlorocarbonyl-1-(phenylsulfonyl)-indole [XXIII] (Ketcha DM, Gribble GW, J. Org. Chem. 1985;50:5451-5457) with an excess of benzylamine in CH_2Cl_2) (method of Ketcha and Gribble) gave *N*-benzyl-1-(phenylsulfonyl)indole-3-carboxamide [XXIV: $R_8 = CH_2Ph$]; mp (MeOH) 188-189°C.

^1H NMR ($CDCl_3$): δ 8.05 (1H, s, H-2), 8.03-7.86 (4H, m, ArH), 7.56-7.26 (10H, m, ArH), 6.43 (1H, m, NH), 4.64 (2H, d, J = 5.7 Hz, CH_2).

Analysis calculated for $C_{22}H_{18}N_2O_3S$ requires:
C, 67.7; H, 4.5; N, 7.2; S, 8.2%.
Found: C, 67.4; H, 4.8; N, 7.1; S, 8.2%.

A solution of the above *N*-benzyl-1-(phenylsulfonyl)indole-3-carboxamide [XXIV: $R_8 = CH_2Ph$] (4.2 g, 11 mmol) in dry THF (200 mL) was treated at -78°C with a solution of 2.5 M n-BuLi in hexanes (9.1 mL, 23 mmol), and the stirred mixture was allowed to warm to -20°C for 15 minutes, before being recooled to -78°C, when it was treated with methyldisulfide (2.5 mL, 28 mmol). The mixture was allowed to warm to 20°C, then quenched with water (25 mL). Volatiles were removed under reduced pressure, and the residue was extracted with EtOAc. Workup of the organic layer gave

a crude product. This was dissolved in MeOH (300 mL), mixed with a solution of K_2CO_3 (6.9 g, 50 mmol) in water (125 mL), and heated under gentle reflux under N_2 for 2 hours to ensure complete hydrolysis of the phenylsulfonyl group (J. Org. Chem. 1985;50:5451-5457). MeOH was removed under reduced pressure, and the residue was diluted with water and extracted with CH_2Cl_2. Chromatography of the resulting oil on Al_2O_3 (eluting with CH_2Cl_2) gave *N*-benzyl-2-(methylthio)-indole-3-carboxamide [XXV: R_8 = CH_2Ph] (2.8 g, 88% yield) as an oil.

^1H NMR ($CDCl_3$): δ 10.65 (1H, s, H-1), 8.29 (d, J = 5.1 Hz, H-4), 7.87 (1H, t, J = 5.6 Hz, CONH), 7.34-7.08 (8H, m, ArH), 4.73 (2H, d, J = 5.6 Hz, CH_2), 2.33 (3H, s, SMe).

^{13}C NMR ($CDCl_3$): δ 165.6 (C=0), 138.5, 136.4, 133.1 and 110.8 (C), 128.5, 127.2, 127.1, 122.9, 121.4, 126.8 and 111.2 (CH), 43.2 (CH_2), 18.5 (CH_3).

HREIMS calculated for $C_{17}H_{16}N_2OS$:

296.0983.

Found: 296.0985.

A solution of the above *N*-benzyl-2-(methylthio)-indole-3-carboxamide [XXV: R = CH_2Ph] (0.85 g, 2.87 mmol) in DMA (5 mL) was added under N_2 to a stirred suspension of MeSLi (0.93 g, 17.2 mmol) in DMA (10 mL). After warming at 80°C for 6 hours, the mixture was acidified with 3N HCl, extracted with CH_2Cl_2, and worked up. Traces of DMA were removed under high vacuum, and the residue was dissolved in MeOH (15 mL) and treated dropwise with H_2O_2 (0.5 mL of 30% solution). After chilling at -30°C overnight, the precipitate was filtered off to give 2,2'-dithiobis[*N*-benzylindolyl-3-carboxamide] (**125**) [V: R_1 = R_3 = H, R_2 = $CONHCH_2Ph$], (74%); mp 203-205°C.

^{1}H NMR (($(CD_3)_2SO$): δ 12.97 (1H, s, NH), 8.48 (1H, t, J = 5.7 Hz, CON<u>H</u>CH_2), 7.86 (1H, d, J = 8.2 Hz, H-4), 7.40 (2H, d, J = 8.3 Hz, H-2',6'), 7.34 (3H, dd, J = 8.3, 8.2 Hz, H-7,3',5'), 7.25 (1H, t, J = 8.2 Hz, H-4'), 7.20-7.10 (2H, m, H-5,6), 4.56 (2H, d, J = 5.7 Hz, CONHC<u>H</u>$_2$).

^{13}C NMR: δ 164.71 (CONH), 139.77 (s), 136.69 (s), 135.30 (s), 128.16 (d), 127.15 (d), 126.56 (d), 124.44 (s), 122.63 (d), 120.78 (d), 119.25 (d), 111.60 (d), 110.54 (s), 42.62 (<u>C</u>ONHCH_2).

Analysis calculated for $C_{32}N_{26}N_4O_2S_2$ requires:
C, 68.3; H, 4.7; N, 10.0; S, 11.4%.
Found: C, 68.0; H, 4.8; N, 9.9; S, 11.2%.

<u>Compound 126 of Table 1</u>

Reaction of 3-chlorocarbonyl-1-(phenylsulfonyl)-indole [XXIII] with an excess of aniline as above gave *N*-phenyl-1-(phenylsulfonyl)indole-3-carboxamide [XXIV: R_8 = Ph]; mp (MeOH) 220-222.5°C.

^{1}H NMR: δ ($CDCl_3$) 8.18 (1H, s, H-2), 8.12 (1H, d, J = 7.8 Hz, H-4), 7.99 (1H, d, J = 8.3 Hz, H-7), 7.91 (2H, d, J = 7.9 Hz, ArH), 7.90 (1H, m, NH), 7.65 (2H, d, J = 8.4 Hz, ArH), 7. 57 (1H, t, J = 7.8 Hz, ArH), 7.45 (2H, t, J = 7.8 Hz, ArH), 7.41-7.33 (4H, m, ArH), 7.15 (1H, t, J = 7.4 Hz, H-5).

Analysis calculated for $C_{21}H_{18}N_2O_3S$ requires:
C, 67.0; H, 4.3; N, 7.4; S, 8.5%.
Found: C, 66.9; H, 4.4; N, 7.3; S, 8.5%.

Treatment of this with n-BuLi/methyldisulfide as above gave 2-(methylthio)-*N*-phenylindole-3-carboxamide [XXV: R_8 = Ph] (81%) as an oil.

^{1}H NMR ($CDCl_3$): δ 10.19 (1H, s, H-1), 9.59 (1H, s, CONH), 8.47 (1H, d, J = 6.8 Hz, H-4), 7.80 (2H, d,

J = 8.5 Hz, ArH), 7.43-7.35 (3H, m, ArH), 7.28-7.16 (3H, m, ArH), 2.51 (3H, s, SCH_3).
^{13}C NMR ($CDCl_3$): δ 163.5 (CO), 138.2, 136.1, 132.5, 127.3, 111.2 (CH), 19.1 (CH_3).
HREIMS calculated for $C_{16}H_{14}N_2OS$:
282.0827
Found: 282.0827.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-phenylindolyl-3-carboxamide] (**126**) [V: $R_1 = R_3 = H$, R_2 = CONHPh], (67%); mp 220-223°C.
^1H NMR ($(CD_3)_2SO$): δ 12.73 (1H, s, NH), 9.88 (1H, s, CONH), 7.81 (1H, d, J = 7.9 Hz, H-4), 7.69 (2H, d, J = 8.4 Hz, H-2',6'), 7.46 (1H, d, J = 7.7 Hz, H-7), 7.34 (2H, dd, J = 8.4, 8.3 Hz, H-3',5'), 7.24 (1H, dd, J = 7.7, 7.7 Hz, H-6), 7.17 (1H, dd, J = 7.9, 7.7 Hz, H-5), 7.10 (1H, dd, J = 8.3 Hz, H-4').
^{13}C NMR: δ 163.27 (CONH), 138.89 (s), 136.73 (s), 133.94 (s), 128.53 (d), 125.12 (s), 123.49 (d), 123.17 (d), 120.99 (d), 120.32 (d), 119.97 (d), 112.89 (s), 111.67 (d).
Analysis calculated for $C_{30}H_{22}N_4O_2S_2$ requires:
C, 67.4; H, 4.2; N, 10.5; S, 12.0%.
Found: C, 67.1; H, 4.3; N, 10.6; S, 12.0%.

Compound 127 of Table 1

Reaction of 3-chlorocarbonyl-1-(phenylsulfonyl)-indole [XXIII] with an excess of methylamine as above gave *N*-methyl-1-(phenylsulfonyl)indole-3-carboxamide [XXIV: R_8 = Me]; mp (MeOH) 192.5-195°C.
^1H NMR ($CDCl_3$): δ 8.06 (1H, s, H-2), 8.03-7.84 (4H, m, ArH) 7.53-7.26 (5H, m, ArH), 6.37 (1H, m, NH), 2.99 (d, J = 4.9 Hz, CH_3).

Analysis calculated for $C_{16}H_{14}N_2O_3S$ requires:
C, 61.1, H, 4.5; N, 8.9; S, 10.2%.
Found: C, 61.1; H, 4.7; N, 8.9; S, 10.0%.

Treatment of this with n-BuLi/methyldisulfide as above gave *N*-methyl-2-(methylthio)indole-3-carboxamide [XXV: R_8 = Me] (95%); mp (hexane-CH_2Cl_2) 138.5-139.5°C.

^{1}H NMR ($CDCl_3$): δ 10.31 (1H, s, H-1), 8.35-8.26 (1H, m, H-4), 7.44 (1H, t, *J* = 4.8 Hz, NH), 7.38-7.30 (1H, m, ArH), 7.19-7.11 (2H, m, ArH), 3.06 (3H, d, *J* = 4.8 Hz, CH_3), 2.49 (3H, s, SCH_3).

^{13}C NMR ($CDCl_3$): δ 166.4 (CO), 136.4, 132.4, 127.4 and 111.7 (C), 123.1, 121.5, 121.2, 111.1 (CH), 26.3 and 18.9 (CH_3).

Analysis calculated for $C_{11}H_{12}N_2OS$ requires:
C, 60.0; H, 5.5; N, 12.7; S, 14.6%.
Found: C, 59.8; H, 5.7; N, 12.7; S, 14.5%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-methylindolinyl-3-carboxamide] (127) [V: R_1 = R_3 = H, R_2 = CONHMe], (57% yield); mp 232-236°C (dec).

^{1}H NMR ($(CD_3)_2SO$): δ 12.94 (1H, s, NH), 7.85 (1H, br, CONH), 7.81 (1H, d, *J* = 8.0 Hz, H-4), 7.46 (1H, d, *J* = 8.0 Hz, H-7), 7.20 (1H, dd, *J* = 8.0, 7.7 Hz, H-6), 7.14 (1H, dd, *J* = 8.0, 7.7 Hz, H-5), 2.88 (3H, d, *J* = 4.5 Hz, $CONHCH_3$).

^{13}H NMR: δ 165.20 (CONH), 136.70 (s), 134.76 (s), 124.47 (s), 122.61 (d), 120.71 (d), 119.55 (d), 111.55 (d), 111.02 (s), 26.22 ($CONH\underline{C}H_3$).

Analysis calculated for $C_{20}H_{18}N_4O_2S_2$ requires:
C, 58.5; H, 4.4; N, 13.7; S, 15.6%.
Found: C, 58.4; H, 4.7; N, 13.6; S, 15.4%.

Compound 128 of Table 1

A solution of 2-(methylthio)-*N*-phenyl-1*H*-indole-3-carboxamide [XXV: R_8 = H] (1.8 g, 6.4 mmol) in EtOH (400 mL) was treated with 3-(dimethylamino)propyl chloride hydrochloride (10.0 g, 64 mmol) and K_2CO_3 (13 g, 96 mmol) and heated under reflux for 3 hours. A further 10 equivalents of the reagents were then added, and the mixture was heated under reflux for a further 48 hours. EtOH was removed under reduced pressure, and the residue was diluted with water to give crude product. This was chromatographed on alumina, eluting with CH_2Cl_2 containing 0.2% MeOH, to give 1-[3-(dimethylamino)propyl]-2-(methylthio)-*N*-phenyl-1*H*-indole-3-carboxamide [XXVI: R_8 = H, R_9 = $(CH_2)_3NMe_2$] (0.49 g, 21%) as an oil.
^{1}H NMR ($CDCl_3$): δ 9.93 (1H, s, NH), 8.54 (1H, d, *J* = 7.8 Hz, H-4), 7.74 (2H, d, *J* = 8.6 Hz, H-2',6'), 7.42-7.24 (5H, m, ArH), 7.11 (1H, t, *J* = 7.4 Hz, ArH), 4.46 (2H, t, *J* = 7.4 Hz, 1-CH_2), 2.47 (3H, s, SCH_3), 2.37 (2H, t, *J* = 6.9 Hz, CH_2N), 2.27 (6H, s, $N(CH_3)_2$), 1.97 (2H, dxt, *J* = 7.4, 6.9 Hz, $CH_2CH_2CH_2$).
^{13}C NMR: δ 162.6 (CO), 138.8, 136.7, 131.4, 127.5, 114.1 (C), 129.0, 124.1, 123.7, 122.8, 122.1, 119.8, 110.0 (CH), 56.5, 42.0, 28.3 (CH_2), 45.3 ($N(CH_3)_2$), 21.1 (SCH_3).
Analysis calculated for $C_{21}H_{25}N_3O_8$ requires:
$[M + H^+]$ = 368.1797.
HRFABMS Found: $[M + H^+]$ = 368.1812.

This was treated with MeSLi at 80°C for 8 hours as above. Water was added, the mixture was washed with CH_2Cl_2, and the aqueous portion was carefully neutralized with 3N HCl and extracted with CH_2Cl_2. This extract was worked up to give an oil which was dissolved in MeOH and treated dropwise at room

temperature with a saturated solution of I_2 in CH_2Cl_2 until no starting material was evident on TLC analysis. The reaction mixture was absorbed directly onto silica and chromatographed. MeOH/EtOAc (1:9) eluted foreruns, while MeOH/EtOAc (1:9) containing a trace of concentrated NH_4OH gave 2,2′-dithiobis[1-{3-(dimethylamino)}propyl)-*N*-phenyl-1*H*-indole-3-carboxamide] (**128**) [V: R_1 = H, R_2 = CONHPh, R_3 = $(CH_2)_3NMe_2$] (10% yield) as a yellow foam.

^{1}H NMR (CD_3OD): δ 8.19 (1H, d, *J* = 7.3 Hz, H-4), 7.64 (1H, d, *J* = 7.5 Hz, H-7), 7.30-7.20 (3H, m, ArH), 7.10-6.95 (4H, m, ArH), 4.41 (2H, t, *J* = 6.2 Hz, CH_2N), 2.74 (2H, t, *J* = 6.7 Hz, CH_2NMe_2), 2.64 (6H, s, $N(CH_3)_2$), 2.09 (2H, m, $CH_2CH_2CH_2$).

Analysis calculated for $C_{40}H_{45}N_6O_2S_2$ requires: $[M + H^+]$ = 705.3045.

HRFABMS found: $[M + H^+]$ = 705.3035.

EXAMPLE K

Preparation of Compound 129 of Table 1 by the Method Outlined in Scheme 10

To a stirred 25°C solution of 41 mL (558 mmol) of DMF and 75 mL of dichloromethane was added dropwise a solution of 133.5 g (465 mmol) of $POBr_3$ in 100 mL of dichloromethane at such a rate to maintain a gentle reflux via the exothermic reaction (ca. 1 hour). The resulting thick tan suspension was stirred vigorously for 10 minutes, then treated dropwise over 20 minutes with a solution of 27.38 g (186 mmol) of 1-methyl-2-indolinone [VII: R_1 = H, R_3 = CH_3) in 55 mL of dichloromethane. The mixture was heated at reflux for 3.5 hours, cooled to 25°C, and the supernatant was decanted and concentrated to a thick reddish brown oil. This was combined with the solids above and treated

very cautiously with portionwise addition of ca. 20 g of ice, then with 112 g of 50% (w/w) aqueous NaOH, all the while keeping the temperature between 30-40°C (pH = 3). An additional 20 g of 50% NaOH, then 100 mL of ice water were added, and the precipitate was collected by filtration. The solids were washed well with water, then dried over P_2O_5 to leave 42.6 g of crude bromoaldehyde; mp 92-97°C. The solids were dissolved in ca. 65 mL of dichloromethane and the solution filtered over 165 g of flash silica gel placed in a 600 mL sintered glass funnel. The frit was washed with dichloromethane until all the product had eluted. The combined product fractions were concentrated to leave 34.66 g (78%) of nearly pure 2-bromo-1-methylindole-3-carboxaldehyde [XXVI: R_1 = H, R_3 = CH_3, X = Br]; mp 110-112° which was used directly in the next reaction.

To a vigorously stirred solution of 2.38 g (10 mmol) of 2-bromo-1-methylindole-3-carboxaldehyde [XXVI: R_1 = H, R_3 = CH_3, X = Br], 10 mL of 2-methyl-2-butene, and 40 mL of p-dioxane at 25°C was added dropwise over ca. 15 minutes a solution of 5 g (55 mmol) of sodium chlorite and 5 g (36 mmol) of $NaH_2PO_4 \cdot H_2O$ in 25 mL of water. The solution was maintained at 25°C. After 3.5 hours, the mixture was treated with an additional 2.5 g each of the chlorite and phosphate. After a total reaction time of 24 hours, the mixture was extracted 3 times with dichloromethane, then the aqueous phase was acidified to pH 2 with aqueous HCl, and extracted once more. The combined organic extracts were washed with water, dried, and evaporated to leave a solid residue that was boiled in 2-propanol. After cooling, the solids were collected by filtration, washed with a little

2-propanol, and dried to leave 2.21 g (87%) of 2-bromo-1-methylindole-3-carboxylic acid [XXVII: R_1 = H, R_3 = CH_3, X = Br] as a beige solid; mp ca. 198°C (dec), in 2 crops.

A suspension of 2.54 g (10 mmol) of 2-bromo-1-methylindole-3-carboxylic acid [XXVII: R_1 = H, R_3 = CH_3, X = Br], 2.54 g (10 mmol) of bis(2-oxo-3-oxazolidinyl)phosphinic chloride, 2.78 mL (20 mmol) of triethylamine, and 25 mL of 1,2-dichloroothane was heated at reflux for 1.5 hours. The mixture was cooled and poured into 150 mL 5% aqueous sodium bicarbonate solution and stirred for 30 minutes. The mixture was extracted with dichloromethane (3 times), the combined organic phase washed with water, brine, dried ($MgSO_4$), and concentrated to leave a red oil. The oil was triturated in ethyl acetate:hexanes and the solids were collected by filtration to give 0.95 g of a side product; mp 227-228°C (dec). The filtrate was concentrated to a viscous oil that was dissolved into chloroform and adsorbed into 9 g of flash SiO_2. This was introduced onto a column containing flash SiO_2 and the column was eluted with hexanes:ethyl acetate (95:5). Product fractions were pooled, concentrated, and triturated from isooctane to give 1.96 g (63%) of 2-bromo-1-methylindole-3-carboxylic acid, t-butyl ester [XXVIII: R_1 = H, R_2 = COO-t-butyl, R_3 = CH_3] as a white solid; mp 87-88°C.

Analysis calculated for $C_{14}H_{16}BrNO_2$ requires:
C, 54.21; H, 5.20; N, 4.52; Br, 25.76%.
Found: C, 54.28; H, 5.20; N, 4.49, Br, 25.83%.

An ice-cold suspension of 119 mg (1.5 mmol) of elemental selenium in 2 mL of THF under N_2 was treated dropwise with 1.1 mL of methyl lithium:lithium bromide

complex (1.5 M in ether). The flask was opened to the air and with a brisk stream of N_2, the resultant white suspension was warmed to ca. 85°C to distill off the ether and most of the THF. The residual semi-solid was cooled in an ice bath and diluted with 1.5 mL of DMA followed by 155 mg (0.5 mmol) of 2-bromo-1-methylindole-3-carboxylic acid, t-butyl ester. The resultant solution was stirred at room temperature for 24 hours, cooled to 0°C, then treated with 2 mL of dilute acetic acid. The mixture was diluted with water and extracted with chloroform (3 x 10 mL). The combined extracts were washed with water (4 times), dried (Na_2SO_4), and concentrated to leave a golden solid. The solid was suspended in 2.3 mL of 2:1 v/v HOAc:H_2O and the suspension was treated with 154 mg of NaBO3·$4H_2O$, then stirred at 25°C for 30 minutes. The solids were collected by filtration, washed with water, and dried to leave 119 mg (77 %) of 2,2'-diselenobis [1-methyl-1H-indole-3-carboxylic acid, t-butyl ester] (129) [XXIX: R_1 = H, R_2 = COO-t-butyl, R_3 = CH_3]; mp 187-189°C.

^{1}H NMR ($CDCl_3$): ∂ 8.13 (1H, dd, J = 0.7, 7.9 Hz, H-4), 7.31-7.19 (3H, m, ArH), 3.63 (3H, s, NCH_3), 1.44 (9H, s, $C(CH_3)_3$).

Analysis calculated for $C_{28}H_{32}N_2O_4Se_2 \cdot 0.2H_2O$ requires:
C, 54.06; H, 5.25; N, 4.50%.
Found: C, 54.40; H, 5.48; N, 4.11%.

<u>Compound 130 of Table 1</u>

To an ice-cold solution of 4 mL of trifluoroacetic acid under nitrogen was added 420 mg (0.68 mmol) of 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid, t-butyl ester] (101) [XXIX: R_1 = H, R_2 = COO-t-butyl, R_3 = CH_3]. The suspension was maintained at 0°C for

3 hours, then poured into ice water. The solids were collected by filtration, washed well with water, and dried to leave 361 mg of product; mp 165°C (dec). The solids were suspended into 80 mL 10% aqueous NH_4OH and the insolubles were removed by filtration. The filtrate was adjusted to pH 3 with 6N aqueous HCl, and the precipitated solids were collected by filtration, washed with water, and dried to leave 268 mg (78%) of 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid] (130) [XXIX: R_1 = H, R_2 = COOH, R_3 = CH_3]; mp 174°C (dec) as an orange solid.

^{1}H NMR ($(CD_3)_2SO$): ∂ 12.35 (1H, s, $CO_2\underline{H}$), 8.04 (1H, d, J = 7.9 Hz, H-4), 7.56 (1H, d, J = 8.4 Hz, H-7), 7.31-7.20 (2H, m, ArH), 3.63 (3H, s, NCH_3).

Analysis calculated for $C_{20}H_{16}N_2O_4Se_2 \cdot 0.1H_2O$ requires:
C, 47.28; H, 3.21; N, 5.51%.
Found: C, 47.20; H, 3.20; N, 5.12%.

<u>Compound 131 of Table 1</u>

A 25°C suspension of 2.79 g (11 mmol) of 2-bromo-1-methylindole-3-carboxylic acid [XXVII: R_1 = H, R_3 = CH_3, X = Br] in 13 mL of 1,2-dichloroethane was treated dropwise with 2.41 mL (33 mmol) of thionyl chloride. The mixture was heated at 75°C for 2 hours. The solution was concentrated to a solid which was co-evaporated once with dichloromethane. The solid was ice-cooled and treated rapidly with 26 mL of 40% aqueous methylamine. The bath was removed and the suspension was stirred at 25°C for 2 hours. The solids were collected by filtration, washed well with water, and dried at 200 mm/70°C/12 hours over P_2O_5 to leave 2.2 g (75%) of product; mp 154-157°C.
Recrystallization from MeOH provided 1.91 g of pure 2-bromo-1-methylindole-3-N-methylcarboxamide

[XXX: R_1 = H, R_3 = CH_3, R_7 = H, R_8 = CH_3] as a beige solid; mp 159-160°C in three crops.

An ice-cold solution of lithium methyl selenide in 2 mL of DMA, made up as previously described from 237 mg (3 mmol) of elemental Se and 2.2 mL of methyllithium (1.5 M in ether) in 3 mL of THF, was treated with 267 mg (1.0 mmol) of 2-bromo-1-methylindole-3-N-methylcarboxamide [XXX: R_1 = H, R_3 = CH_3, R_7 = H, R_8 = CH_3]. The resultant solution was stirred at room temperature for 3.5 hours, cooled to 0°C, then treated with 5% aqueous HCl. The mixture was extracted with dichloromethane (2 x 10 mL), the combined extracts washed with water (2 times), then concentrated in vacuo to leave an oil that was dissolved in methanol. The solution was ice-cooled and treated with 113 µL of 30% aqueous H_2O_2. After stirring for 10 minutes, the resultant suspension was filtered, and the solids were washed with 2-propanol and dried to leave 183 mg (67%) of 2,2'-diselenobis [N,1-dimethyl-1H-indole-3-carboxamide] (131) [XXIX: R_1 = H, R_2 = $CONHCH_3$, R_3 = CH_3] as a yellow solid; mp 225-230°C (dec).

^1H NMR ($CDCl_3$ + $(CD_3)_2SO$): ∂ 7.97 (1H, d, J = 7.9 Hz, H-4), 7.39-7.18 (3H, m, ArH), 6.84 (1H, s, N$\underline{H}CH_3$), 3.85 (3H, s, indole NCH_3), 2.12 (3H, d, J = 4.5 Hz, $NHC\underline{H}_3$).

Analysis calculated for $C_{22}H_{22}N_4O_2Se_2 \cdot 0.9H_2O$ requires:

C, 48.17; H, 4.37; N, 10.21%.

Found: C, 48.20; H, 4.22; N, 10.28%.

<u>Compound 132 of Table 1</u>

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXVII: R_1 = H, R_3 = CH_3, X = Cl] with $SOCl_2$ as described in Example I and reaction of this with 3 equivalents of N,N-diethylethylenediamine

in dichloromethane at 0°C followed by workup gave 2-chloro-1-methylindole-3-N-(2-(diethylamino)ethyl)-carboxamide [XXX: R_1 = H, R_6 = H, R_7 = $(CH_2)_2NEt_2$, X = Cl] as a soft solid in 68% yield, used without further purification.

Treatment of this with lithium methyl selenide as described above gave 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1-methyl-1H-indole-3-carboxamide] **(132)** [XXIX: R_1 = H, R_2 = $CONH(CH_2)_2NEt_2$, R_3 = CH_3] (68% yield); mp 128-130°C. Reaction of the free base with excess hydrogen chloride in 2-propanol followed by concentration to an oil and crystallization at 25°C gave the compound as a dihydrochloride salt (18% yield); mp 160-164°C.

^1H NMR ($(CD_3)_2SO$): ∂ 10.13 (1H, s, $^+N\underline{H}(CH_2CH_3)_2$), 8.14-8.11 (1H, m, CON$\underline{H}$), 7.89 (1H, d, J = 8.2 Hz, H-4), 7.57 (1H, d, J = 8.4 Hz, H-7), 7.34-7.17 (2H, m, ArH), 3.63 (3H, s, $NC\underline{H}_3$), 3.17-3.14 (2H, m, $CONHC\underline{H}_2$), 3.06-3.00 (4H, m, $N(C\underline{H}_2CH_3)_2$), 2.86 (2H, t, J = 6.5 Hz, $CONHCH_2C\underline{H}_2$), 1.16 (6H, t, J = 7.2 Hz, $N(CH_2C\underline{H}_3)_2$).

Analysis calculated for $C_{32}H_{44}N_6O_2Se_2 \cdot 2.0HCl \cdot 1.7H_2O$ requires:

C, 47.67; H, 6.18; N, 10.42; Cl^-, 8.79%.

Found: C, 47.71; H, 6.12; N, 10.35; Cl^-, 8.97%.

<u>Compound 133 of Table 1</u>

A mechanically stirred suspension of 15 g (83.5 mmol) of 2-chloroindole-3-carboxaldehyde [XXVI: R_1 = R_3 = H, X = Cl] (Schule, et al., <u>Arch. Pharm.</u> [Weinheim] 1972;305:523-533), 84 mL of 2-methyl-2-butene, and 200 mL of p-dioxane in an ice bath was treated with a solution of 40 g each of sodium chlorite and sodium dihydrogen phosphate monohydrate in 200 mL of water. The biphasic mixture was then stirred

vigorously at 25°C for 3.5 hours. An additional 16 g each of solid sodium chlorite and sodium dihydrogen phosphate monohydrate was added and the mixture was stirred for another 3.5 hours. The mixture was diluted with 350 mL of ethyl acetate and 200 mL of water. The layers were separated and the aqueous phase was extracted with 300 mL of ethyl acetate. The combined organic extracts were extracted with cold 2% aqueous NaOH (3 x 200 mL). The basic extracts were combined and acidified to pH 4 with 6N aqueous HCl. The precipitated solids were collected by filtration, washed well with water, and air dried overnight. The solids were dissolved in 150 mL of hot acetone and the solution was treated with 65 mL of hexane. After storage at 3°C for 20 hours, the solids were collected by filtration, washed with cold acetone, and dried to leave 7.71 g of pure 2-chloroindole-3-carboxylic acid [XXVII: $R_1 = R_3 = H$, $X = Cl$] as an off-white solid; mp 181.5°C (dec). Further processing of the filtrate as above afforded 2.41 g of a second crop; mp 179.5°C (dec). Total yield 10.12 g (62%).

The acid chloride of 2-chloroindole-3-carboxylic acid [XXVII: $R_1 = R_3 = H$, $X = Cl$] was made via $SOCl_2$ as described above. Reaction of this with a saturated solution of anhydrous methylamine in THF at 0°C gave 2-chloroindole-3-N-methylcarboxamide [XXX: $R_1 = R_3 = H$, $R_6 = H$, $R_7 = CH_3$, $X = Cl$]; mp 234-236°C, in 51% yield.

Reaction of this with lithium methyl selenide as described above gave 2,2'-diselenobis[N-methyl-1H-indole-3-carboxamide] (133) [XXIX: $R_1 = R_3 = H$, $R_3 = CONHCH_3$] (20% yield), mp 272-275°C (decomp). ^1H NMR ($(CD_3)_2SO$): δ 12.36 (1H, s, indole NH), 7.83 (1H, d, J = 7.7 Hz, H-4), 7.79 (1H, d, J = 4.1, N$\underline{H}CH_3$),

7.48 (1H, d, J = 7.7 Hz, H-7), 7.16-7.07 (2H, m, ArH), 2.90 (3H, d, J = 4.1 Hz, NHC$\underline{H}_3$).
Analysis calculated for $C_{20}H_{18}N_4O_2Se_2 \cdot 0.9H_2O$ requires: C, 46.15; H, 3.83; N, 10.76%.
Found: C, 46.08; H, 3.44; N, 10.45%.

Compound 134 of Table 1

The acid chloride of 2-chloroindole-3-carboxylic acid [XXVII: $R_1 = R_3 = H$, X = Cl] was made via $SOCl_2$ as described above. Reaction of this with 3 equivalents of N,N-diethylethylenediamine in ether as described above followed by workup gave 2-chloroindole-3-N-(2-(diethylamino)ethyl)carboxamide [XXX: $R_1 = R_3 = R_6 = H$, $R_7 = (CH_2)NEt_2$, X = Cl]; mp 99-108°C in 38% yield.
^{1}H NMR ($CDCl_3$): ∂ 11.50 (1H, s, indole NH), 8.19 (1H, d, J = 6.5 Hz, H-4), 7.33 (1H, d, J = 8.4 Hz, H-7), 7.21-7.15 (3H, m, ArH and CON$\underline{H}$), 3.54 (2H, q, J = 5.3 Hz, CONHC$\underline{H}_2$), 2.69 (2H, t, J = 6.0 Hz, CONHCH$_2$C$\underline{H}_2$), 2.59 (4H, q, J = 7.2 Hz, N(C$\underline{H}_2$CH$_3$)$_2$), 1.05 (6H, t, J = 7.2 Hz, N(CH$_2$C$\underline{H}_3$)$_2$).

Reaction of this with lithium methyl selenide as described above gave 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1H-indole-3-carboxamide] (**134**) [XXIX: $R_1 = R_3 = H$, $R_2 = CONH(CH_2)_2NEt_2$] (44% yield); mp 225-226°C (dec). Salt formation as above gave the compound as the dihydrochloride salt (85% yield); mp 257-259°C (dec).
^{1}H NMR ($(CD_3)_2SO$): ∂ 12.75 (1H, s, indole NH), 10.08 (1H, s, $^+$N$\underline{H}$(CH$_2$CH$_3$)$_2$), 8.09 (1H, t, J = 5.7 Hz, CON$\underline{H}$), 7.93 (1H, d, J = 8.9 Hz, H-4), 7.51 (1H, d, J = 6.8 Hz, H-7), 7.19-7.12 (2H, m, ArH), 3.78-3.73 (2H, m, CONHC$\underline{H}_2$), 3.32 (2H, t, J = 6.5 Hz, CONHCH$_2$C$\underline{H}_2$),

3.29-3.20 (4H, m, N($C\underline{H}_2CH_3)_2$), 1.26 (6H, t, J = 7.2 Hz, N($CH_2C\underline{H}_3)_2$).
Analysis calculated for $C_{30}H_{40}N_6O_2Se_2 \cdot 2.0HCl \cdot 1.0H_2O$ requires:
C, 47.07; H, 5.79; N, 10.98; Cl^-, 9.26%.
Found: C, 47.01; H, 5.70; N, 10.56; Cl^-, 8.87%.

Compound 135 of Table 1

A mixture of 2.09 g (10 mmol) of 2-chloroindole-3-N-methylcarboxamide [XXX: $R_1 = R_3 = R_6 = H$, $R_7 = CH_3$, X = Cl], 1.72 g (10 mmol) of 2-diethylaminoethyl chloride hydrochloride (n = 2, Q = Cl, $R_8 = R_9$ = Et), 7.5 g (23 mmol) of anhydrous cesium carbonate, 3 g of activated 3A molecular sieves, and 20 mL of acetone was stirred under nitrogen at 25°C for 16 hours. The mixture was filtered over celite and the filtrate was concentrated to a solid that was partitioned between chloroform and water. The organic phase was dried (Na_2SO_4) and concentrated to a residue that was crystallized from ethyl acetate:hexanes (5:8). The solids were collected and dried to leave 1.43 g of 2-chloro-1-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide [XXX: $R_1 = R_6 = H$, $R_3 = (CH_2)_2NEt_2$, $R_7 = CH_3$, X = Cl]; mp 103-104°C, in 46% yield.
^1H NMR ($CDCl_3$): ∂ 8.24 (1H, d, J = 8.0 Hz, H-4), 7.33-7.21 (3H, m, ArH), 6.35 (1H, s, CON$\underline{H}CH_3$), 4.27 (2H, t, J = 7.6 Hz, 1-N$C\underline{H}_2$), 3.06 (3H, d, J = 4.8 Hz, CONH$C\underline{H}_3$), 2.73 (2H, t, J = 7.5 Hz, 1-NH$CH_2C\underline{H}_2$), 2.62-2.55 (4H, m, N($C\underline{H}_2CH_3)_2$), 1.02 (6H, t, J = 7.0 Hz, N($CH_2C\underline{H}_3)_2$).

Reaction of this with lithium methyl selenide as described above gave 2,2'-diselenobis[1-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide] (135)

[XXIX: R_1 = H, R_2 = $CONHCH_3$, R_3 = $(CH_2)_2NEt_2$] (63% yield); mp 156-157°C.

Analysis calculated for $C_{32}H_{44}N_6O_2Se_2 \cdot 0.5H_2O$ requires:
C, 54.01; H, 6.37; N, 11.81%.
Found: C, 54.14; H, 6.23; N, 11.54%.

EXAMPLE L

Preparation of Compound 136 of Table 1 by the method outlined in Scheme 11.

An ice-cold solution of 15 g (50 mmol) of the *N*-trifluoroacetamide of D-tryptophan, synthesized by methods previously outlined (J. Org. Chem. 1979;44:2805-2807) in 50 mL of THF under N_2 was treated sequentially with 7.1 g (52.5 mmol) of 1-hydroxybenzotriazole then 10.83 g (52.5 mmol) of 1,3-dicyclohexylcarbodiimide. After 15 minutes, the solution was treated with 5.74 mL (52.6 mmol) of benzylamine. The solution was maintained at 0-5°C for 1 hour, then let warm to 25°C overnight. The mixture was filtered and the collected solids were washed with ethyl acetate. The filtrate was concentrated to an oil that was dissolved in 250 mL of ethyl acetate. The solution was washed sequentially with 250 mL portions of 10% aqueous acetic acid, water, 5% aqueous sodium hydrogen carbonate, water and brine, then dried ($NaSO_4$), and concentrated to a solid. Crystallization from 170 mL of 65:35 2-propanol:petroleum ether afforded 12.81 g (66%) of (R)-*N*-(phenylmethyl)-α-[(trifluoroacetyl)-amino]-1*H*-indole-3-propanamide [II: R_1 = H, R_2 = $CH_2CH(NHCOCF_3)CONHCH_2Ph$, R_3 = H] as an off-white solid which was used directly in the next reaction; mp 186-188°C.

To an ice-cold solution of 10 g (25.7 mmol) of (R)-*N*-(phenylmethyl)-α-[(trifluoroacetyl)amino]-

1*H*-indole-3-propanamide [XXIX: R_1 = H, R_2 = $CH_2CH(NHCOCF_3)CONHCH_2Ph$, R_3 = H] in 70 mL of THF was added dropwise Se_2Cl_2. The resultant deep red suspension was stirred at 0-5°C for 4 hours, then quenched with 300 mL of water. The solids were collected by filtration, washed well with water, and air dried to leave 12 g of impure product as an orange solid. A portion of this material (10.7 g) was dissolved in 100 mL of methanol and the solution under N_2 was cooled in an ice bath. Sodium borohydride (ca 1 g) was added portionwise until there was no more color discharge. The mixture was poured immediately into a N_2 purged separatory funnel containing 200 mL of ether. The mixture was diluted with 200 mL of water, the mixture shaken, and the phases separated. The aqueous layer was treated with a small portion of additional sodium borohydride, extracted again with ether, ice-cooled, then acidified to pH 1 with concentrated HCl. The aqueous phase was extracted twice with ethyl acetate, then the combined extracts were dried ($MgSO_4$) and filtered through a pad of flash silica gel. The filtrate was concentrated to leave 5.91 g of a foam that was dissolved in ca 40 mL of absolute ethanol. The solution was kept at 25°C for several hours to initiate crystallization, then stored at 5°C. The solids were collected by filtration, washed with 2-propanol, and dried to leave 4.23 g of pure [R-(R*,R*)]-2,2'-diselenobis[*N*-(phenylmethyl)-α-[(trifluoroacetyl)amino]-1*H*-indole-3-propanamide] [XXIX: R_1 = H, R_2 = $CH_2CH(NHCOCF_3)CONHCH_2Ph$, R_3 = H], as a yellow powdery solid; mp 181-185°C.

Analysis calculated for $C_{40}H_{34}N_6O_4F_6Se_2 \cdot H_2O$ requires:

C, 50.43; H, 3.81; N, 8.82%.

Found: C, 50.47; H, 3.57; N, 8.71%.

Further processing of the filtrate by chromatography over flash SiO_2, eluting first with dichloromethane then 7% ethyl acetate in dichloromethane, provided an additional 671 mg of product following crystallization; mp 180-183°C.

A suspension of 233.5 mg (0.25 mmol) of this diselenide in 4.5 mL of dry absolute ethanol was treated with 95 mg (2.5 mmol) of sodium borohydride. The mixture was heated at reflux for 15 minutes, then treated with 95 mg of additional borohydride. The mixture was refluxed for 1.25 hours, then treated with a third 95 mg portion of borohydride. After refluxing for 30 minutes, the mixture was cooled to 25°C, diluted with methanol, and poured into an ice-cold stirring mixture of 6N HCl and ethyl acetate. The resultant mixture was stirred vigorously for 15 minutes, filtered, the phases separated, and the aqueous layer extracted once more with ethyl acetate. The combined ethyl acetate phases were then back extracted with 5% aq HCl (five times). The acidic aqueous layers were combined and diluted with an equal volume of ethyl acetate. While carefully monitoring the pH, the stirred solution was treated carefully with 10% aqueous NaOH until pH = 9.5. The resultant yellow precipitate was collected by filtration, washed well with water, and dried to leave 90 mg of [R-(R*,R*)]-2,2'-diselenobis[α-amino-*N*-(phenylmethyl)-1*H*-indole-3-propanamide] (136) [XXIX: R_1 = H, R_2 = $CH_2CH(NH_2)CONHCH_2Ph$, R_3 = H], as a yellow powder; mp 172-174°C.

^{1}H NMR ($(CD_3)_2SO$): δ 11.62 (1H, s, NH), 8.23 (1H, t, J = 5.1 Hz, N$\underline{H}$CH$_2$), 7.61 (1H, d, J = 8.0 Hz, ArH), 7.38 (1H, d, J = 8.2 Hz, ArH), 7.35-6.95 (7H, m, ArH), 4.20, 4.17 (2x1H, 2xdd, J = 15.2, 5.8 Hz, NHC$\underline{H}_2$), 3.46-3.40

(1H, br m, Ar-$CH_2C\underline{H}$), 3.04-2.98 (1H, br m, Ar-$C\underline{H}$), 2.75-2.68 (1H, br m, Ar-$C\underline{H}$), 1.70 (2H, br s, NH_2).
Analysis calculated for $C_{36}H_{36}N_6O_2Se_2 \cdot 1.5H_2O$ requires:
C, 56.18; H, 5.11; N, 10.68%.
Found: C, 55.91; H, 4.72; N, 10.68%.

Processing of the ethyl acetate layer from the base treatment provided 15 mg of additional product; mp 165-171°C. Total yield = 105 mg (57%).

Compound 137 of Table 1

Starting from the *N*-trifluroracetamide of L-tryptophan (J. Org. Chem. 1979;44:2805-2807) and following the same procedures as outlined for the synthesis of compound **136** of Table 1, there was obtained [S-(R*,R*)]-2,2'-diselenobis[α-amino-*N*-(phenylmethyl)-1*H*-indole-3-propanamide] (**137**) [XXIX: R_1 = H, R_2 = $CH_2CH(NH_2)CONHCH_2Ph$, R_3 = H] as a yellow powder; mp 171°C (dec).

BIOLOGICAL AND BIOCHEMICAL EFFECTS

Tyrosine Kinase Inhibition Assay and Growth Inhibition Effects on Cells in Tissue Culture

Table 2 provides representative data on inhibition of the epidermal growth factor receptor tyrosine kinase, and on cell growth inhibition.

In Table 2: **No.** is the compound number as recorded in Table 1.

IC50 (EGFR TK) is the concentration of drug necessary to reduce incorporation of P^{32} in GAT by 50%.

IC_{50} (PDGFR TK) is the concentration of drug necessary to reduce incorporation of P^{32} in Glu-Tyr by 50%.

IC50 growth Inhibition is (cell growth inhibition) is the concentration of drug necessary to reduce the cellular growth rate by 50%.

TABLE 2. IC_{50} Data for EGRF-R and PDGF-R Inhibition and Cell Growth Inhibition for Selected Compounds of Table 1

No.	IC_{50} (μM) or % Inhibition at 100 μM		Growth Inhibition
	EGRF-R	PDGF-R	
1	14.9	--	
2	26%	--	
3	43%	8.6%	
4	27%	--	
5	4%	--	
6	25	8.5%	
7	1.3	--	94
8	8.5	--	
9	52%	--	16
10	10%	--	34

TABLE 2 (cont'd)

No.	IC_{50} (μM) or % Inhibition at 100 μM		Growth Inhibition
	EGRF-R	PDGF-R	
11	24%	--	
12	3%	--	
13	43%	--	
14	22	--	
15	6.8	--	
16	23	--	
17	12.5%	--	
18	2%	9%	
19	10%	--	
20	9	--	
21	1.0	--	64
22	--	--	
23	--	--	
24	19%	--	
25	8.7	--	
26	23%	5%	
27	17.8	--	2.3
28	33	--	
29	8.3	--	25-100
30	9.3	--	8
31	35.5	--	1
32	34.5	4.7%	36
33	39	16.7%	3.0
34	38	12.8%	2.7
35	16.5	33.9%	
36	4.8	--	59
37	3.3	--	
38	36.5%	--	1.6
39	20.6	--	7.4
40	16.3%	--	5.2
41	8.4	--	>25
42	26%	--	
43	2.9	--	
44	16.6%	5%	2.4
45	1.6	--	
46	11.4%	--	2.7
47	0.85	--	6
48	35.5	--	

TABLE 2 (cont'd)

No.	IC_{50} (μM) or % Inhibition at 100 μM EGRF-R	PDGF-R	Growth Inhibition
49	84.1	--	
50	16.0	62.6%	
51	7.0	--	
52	68.2	18.3%	
53	4.2	--	
54	29	20.6%	
55	44	--	
56	7.3	44.5%	
57	46%	14.5%	
58	68%	--	
59	30.5	11.4%	
60	53%	--	
61	37%	11%	
62	6.0	71%	5.3
63	60	--	
64	29	--	
65	17.8	--	
66	8.3	--	
67	18%	2%	
68	14%	--	1.8
69	55.6%	8.9%	
70	8.6	1%	12
71	20%	5%	52
72	47%	22%	
73	4.3	21%	9.3
74	23%	--	
75	6%	3%	4
76	7%	19%	22
77	9%	1%	
78	27%	7%	
79	11%	20%	1.9
80	0%	16%	
81	3.6	2%	17
82	6.5	--	24
83	22.3	57%	10
84	35%	22%	
85	8%	7%	
86	4.9	5%	

TABLE 2 (cont'd)

No.	IC50 (μM) or % Inhibition at 100 μM		Growth Inhibition
	EGRF-R	PDGF-R	
87	34%	44%	
88	54	51%	
89	11.4	3%	
90	26	36.5	
91	5.2	--	
92	--	--	
93	30%	--	
94	--	--	
95	9.4	--	
96	--	--	
97	10.1	28.1	1.8
98	1.5	9%	5-12
99	40	19%	2.8
100	18%	23%	
101	5.5	--	
102	6.1	--	
103	7%	--	3.8
104	20%	--	
105	16.9	33%	
106	34%	--	
107	12.0	--	
108	20%	--	
109	47	8%	
110	13	--	
111	5.3	76%	
112	10.0	69%	
113	5%	29%	
114	42.9	7.0	
115	26	19.7	>50
116	4%	7.9	
117	25%	4.2	
118	4.7	78%	
119	21.2	73%	
120	6.9	--	
121	5.6	--	
122	51%	--	
123	--	--	
124	--	--	

TABLE 2 (cont'd)

No.	IC_{50} (μM) or % Inhibition at 100 μM		Growth Inhibition
	EGRF-R	PDGF-R	
125	78%	--	
126	60%	--	
127	6.8	--	
128	--	--	
129	31%	--	
130	3.5	--	
131	5.8	--	5.5
132	4.7	--	20
133	13.0	--	<5
134	4.6	--	8
135	6.9		
136			
137			

<u>EGF Receptor Tyrosine Kinase Assay</u>

Membrane vesicles were prepared by the method described in Cohen S, Ushiro H, Stoscheck C, and Chinkers M. A native 170,000 epidermal growth factor receptor-kinase complex from shed plasma membrane vesicles, <u>J. Biol. Chem.</u> 1982;257:1523-1531, and kept frozen at -90°C until use. At the time of assay, membranes were solubilized in 4% Triton X-100 and 10% glycerol. The reaction is carried out in wells of a 96-well microtiter plate in a total volume of 125 L. Buffer containing 20 mM Hepes (pH 7.4), 15 mM $MgCl_2$, 4 mM $MnCl_2$, and 0.02% BSA followed by 5 to 20 mg of membrane protein and 150 ng of epidermal growth factor. The plates are incubated for 10 minutes at room temperature to activate the receptor kinase. 20 g of GAT (random polymer of glycine, alanine, and tyrosine) and 0.2 mCi of α-[P^{32}] ATP plus or minus

compound are added and incubated 10 minutes at room temperature. The reaction is stopped by addition of 125 mL of 30% TCA, precipitate washed twice with 200 mL of 15% TCA on 0.65 micron filters, and the filters counted by scintillation spectrometry.

PDGF Receptor Tyrosine Kinase Inhibition Assay

Recombinant baculovirus containing human PDGF β receptor intracellular tyrosine kinase domain was used to infect SF9 cells to overexpress the protein, and cell lysates were used for the assay. The ability of the tyrosine kinase to phosphorylate glutamate - tyrosine substrate in the presence of P^{32}-ATP and inhibitor was measured by counting the incorporation of P^{32} in Glu-Tyr in TCA precipitable material.

Table 2 provides representative data on inhibition of the PDGF receptor tyrosine kinase. In Table 2, No. refers to the compound number as recorded in Table 1.

DETAILED STUDIES ON THE BIOLOGICAL EFFECTS OF COMPOUNDS 21 AND 70

Effects on Cells in Tissue Culture

Swiss 3T3 fibroblasts, that were growth arrested in serum-free media for 24 hours, were exposed to various concentrations of compound for 2 hours. The cells were then exposed to individual growth factors for 5 minutes and proteins that were phosphorylated on tyrosine in response to the mitogens and were detected by Western blotting techniques using phosphotryosine antibodies. Similar techniques were used for tumor cell lines except the time in serum-free media was increased.

At concentrations of 10 to 50 mM, Compound **21** suppressed: (1) EGF mediated phosphorylation of a variety of endogenous proteins; (2) PDGF mediated autophosphorylation of the PDGF receptor as well as PDGF mediated tyrosine phosphorylation of other endogenous proteins and; (3) bFGF mediated tyrosine phosphorylation. **70** was more selective and inhibited only bFGF mediated tyrosine phosphorylation and at concentrations as low as 2 mM.

Effects on Growth Factor Mediated Mitogenesis

Swiss 3T3 fibroblasts, that were growth arrested in serum-free media for 24 hours, were exposed to various concentrations of compound for 2 hours. The cells were then exposed to individual growth factors for 24 hours and mitogenesis assessed by measuring tritiated thymidine incorporation into DNA.

The concentration of **21** and **70** required to inhibit growth factor mediated mitogenesis by 50% for the following growth factors was as follows:

Growth Factor	IC_{50} (μM) for 21	IC_{50} (μM) for 70
EGF	2	3
PDGF	8	4
bFGF	13	3
serum	19	3

Growth Inhibition Assay

Swiss 3T3 mouse fibroblasts were maintained in dMEM/F12 media containing 10% fetal calf serum. Two mL of cells at a density of 1 x 10⁴/mL were placed in 24-well plates plus or minus various concentrations of

the inhibitor. The cells were grown at 37°C under 5% CO_2 for 72 hours and then counted by Coulter counter. The data were expressed as the concentration of inhibitor necessary to decrease the growth rate by 50%.

Compound 21 was growth inhibitory for a variety of human tumor cell lines as well as the Swiss 3T3 fibroblasts. The concentration of 21 necessary to inhibit cell growth by 50% is shown below:

Cell Line	IC_{50} (μM)
MDA 468 breast	43
A431 epidermoid	62
A549 lung	30
MDV-7 breast	39
MDA-231 breast	15
Swiss 3T3 fibroblasts	64
HT-29 colon	55

Although the carboxyl containing structures are among the most active enzyme inhibitors, they are poorly transported into the cell, whereas the less active esters are transported efficiently and once in the cytoplasm rendered highly active by esterases. Esters may, therefore, be more favorable than carboxylic acids in this invention.

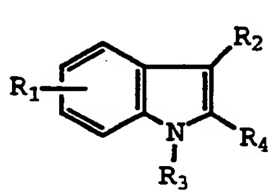
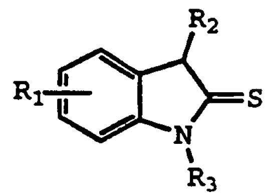
The data of Table 2 show that the 2-thioindoles of general Formula I listed in Table 1 include compounds which are active as potent inhibitors of protein tyrosine kinases and as cytotoxic agents.

The invention is not limited to the particular embodiments shown and described herein, since various changes and modifications may be made without departing

from the spirit and scope of the invention as defined by the following claims.

CLAIMS

1. 2-Thioindole, 2-indolinethione and polysulfide compounds of the group represented by the general Formulas I and IV

 I  IV

and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OCOR, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

C_{2-4} alkyl,
$(CH_2)_nCOOH$,
$(CH_2)_nCOOR$,
$(CH_2)_nCOR$,
$(CH_2)_nSO_2R$,
$(CH_2)_nSO_2NRR$,
$(CH_2)_nSO_2NHR$,
CH=CHCOOH,
$(CH_2)_n\underset{\substack{|\\ OH}}{CH}-COOH$,
$(CH_2)_n\underset{\substack{|\\ NH_2}}{CH}-COOH$,
$(CH_2)_nCONH_2$,
$(CH_2)_nCONHR$,

$(CH_2)_nCONRR$,
$(CH_2)_nCONHCH_2Ph$,
CONHR,
CONRR,
CONHPh,
COY,
COPhCOOH,
COPhCOOR,
$(CH_2)_nCONHPh$,
$(CH_2)_nCONHPhR$,
SO_2Y;

n is an integer from 1 to 4;

R is lower alkyl;

R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SH, S_oX, and S_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl moiety of Formula I provided that the group does not comprise compounds having the names

2-(2-thioxo-3-indolinyl)acetic acid,
2-(1-methyl-2-thioxo-3-indolinyl)acetic acid,
methyl 2-(2-thioxo-3-indolinyl)acetate,
ethyl 2-(1-methyl-2-thioxo-3-indolinyl)-acetate,
bis[methylindolinyl-3-acetate-(2)]disulfide,
bis[indolyl-3-acetic acid-(2)]disulfide,

bis[methylindolyl-3-acetate-(2)]trisulfide, and

bis[1-methylindolyl-3-acetic acid-(2)]-disulfide.

2. A thioindole compound according to Claim 1 selected from

methyl 2-(1-methyl-2-thioxo-3-indolinyl)-acetate,

N-benzyl(2-thioxo-3-indolinyl)acetamide,

3-(2-thioxo-3-indolinyl)propanoic acid,

3-(1-methyl-2-thioxo-3-indolinyl)propanoic acid,

methyl 3-(2-thioxo-3-indolinyl)propanoate,

ethyl 3-(2-thioxo-3-indolinyl)propanoate,

3-(1-methyl-2-thioxo-3-indolinyl)propanoate,

ethyl 3-(1-methyl-2-thioxo-3-indolinyl)-propanoate,

N-benzyl 3-(2-thioxo-3-indolinyl)propanamide,

4-(2-thioxo-3-indolinyl)butanoic acid,

4-(1-methyl-2-thioxo-3-indolinyl)butanoic acid,

methyl 4-(2-thioxo-3-indolinyl)butanoate,

methyl 4-(1-methyl-2-thioxo-3-indolinyl)-butanoate,

N-phenyl (1-methyl-2-thioxo-3-indolinyl)-carboxamide,

N-phenyl (1-methyl-2-methylthio-3-indolinyl) carboxamide,

3-benzoyl-1-methyl-2-indolinethione,

3-(4'-carboxybenzoyl)-1-methyl-2-indolinethione,

3-(4'-carbomethoxybenzoyl)-1-methyl-2-indolinethione,

and pharmaceutically acceptable salts thereof.

3. A polysulfide compound according to Claim 1 selected from

2,2'-dithiobis[methyl 2-(1-methyl-3-indolyl)acetate],

bis[indolyl-3-acetic acid-(2)]trisulfide,

bis[ethyl 1-methylindolyl-3-acetate-(2)]-disulfide,

2,2'-dithiobis[N-benzyl-2-(3-indolyl)-acetamide],

bis[indolyl-3-propanoic acid-(2)]disulfide,

2,2'-dithiobis[3-(1-methyl-3-indolyl)-propanoic acid],

bis[ethylindolyl-3-propanoate-(2)]disulfide,

2,2'-dithiobis[methyl-3-(3-indolyl)-propanoate],

2,2'-dithiobis[methyl-3-(1-methyl-3-indolyl)-propanoate],

bis[5-methylindolyl-3-propanoic acid-(2)]-disulfide,

bis[ethyl-5-methylindolyl-3-propanoate-(2)]-disulfide,

bis[6-methylindolyl-3-propanoic acid-(2)]-disulfide,

bis[ethyl-6-methylindolyl-3-propanoate-(2)]-disulfide,

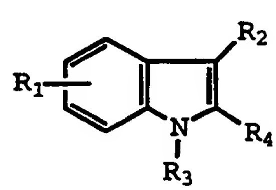
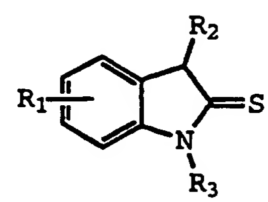
bis[7-methylindolyl-3-propanoic acid-(2)]-disulfide,

bis[ethyl-7-methylindolyl-3-propanoate-(2)]-disulfide,

2,2'-dithiobis[N-benzyl-3-(3-indolyl)-propanamide],
bis[indolyl-3-butanoic acid-(2)]disulfide,
2,2'-dithiobis[4-(1-methyl-3-indolyl butanoic acid],
bis[methyl indolyl-3-butanoate-(2)]disulfide,
bis[methyl 1-methylindolyl-3-butanoate-(2)]-disulfide,
bis[N-phenyl 1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 1-ethylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 4-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 5-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 7-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 1-methyl-7-azaindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 1,4-dimethylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 1,5-dimethylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 1,6-dimethylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 1,7-dimethylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 4-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 5-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-phenyl 6-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide,

bis[N-phenyl 7-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-methyl 1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-benzyl 1-methylindolyl-3-carboxamide-(2)]disulfide,
bis[N-methylphenylsulfonyl)-2-indolyl]-disulfide,
bis[3-benzoyl-1-methylindole-(2)]disulfide,
bis[3-(4'-carboxybenzoyl)-1-methylindole-(2)]-disulfide,
bis[3-(4'-carbomethoxybenzoyl)-1-methylindole(2)]disulfide,
and pharmaceutically acceptable salts thereof.

4. A pharmaceutical composition useful for inhibition of protein tyrosine kinase dependent disease in a mammal, containing in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound selected from 2-thioindole, 2-indolinethione, and polysulfide compounds represented by the general Formulas I and IV

 I  IV

and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and

further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

C_{2-4} alkyl,

$(CH_2)_nCOOH$,

$(CH_2)_nCOOR$,

$(CH_2)_nCOR$,

$(CH_2)_nSO_2R$,

$(CH_2)_nSO_2NRR$,

$(CH_2)_nSO_2NHR$,

CH=CHCOOH,

$(CH_2)_nCH(OH)\text{-}COOH$,

$(CH_2)_nCH(NH_2)\text{-}COOH$,

$(CH_2)_nCONH_2$,

$(CH_2)_nCONHR$,

$(CH_2)_nCONRR$,

$(CH_2)_nCONHCH_2Ph$,

CONHR,

CONRR,

CONHPh,

COY,

COPhCOOH,

COPhCOOR,

$(CH_2)_nCONHPh$,

$(CH_2)_nCONHPhR$,

SO_2Y;

n is an integer from 1 to 4;

R is lower alkyl;

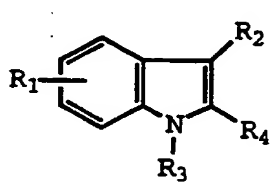
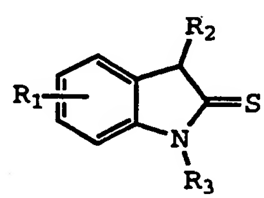
R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally

substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SH, S_oX, and S_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl moiety of Formula I.

5. A pharmaceutical composition useful for treating aberrant cell growth in a mammal containing in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound selected from 2-thioindole, 2-indolinethione, and polysulfide compounds represented by the general Formulas I and IV

 I  IV

and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

C_{2-4} alkyl,
$(CH_2)_nCOOH$,
$(CH_2)_nCOOR$,
$(CH_2)_nCOR$,
$(CH_2)_nSO_2R$,

$(CH_2)_nSO_2NRR$,
$(CH_2)_nSO_2NHR$,
CH=CHCOOH,
$(CH_2)_nCH(OH)\text{-}COOH$,
$(CH_2)_nCH(NH_2)\text{-}COOH$,
$(CH_2)_nCONH_2$,
$(CH_2)_nCONHR$,
$(CH_2)_nCONRR$,
$(CH_2)_nCONHCH_2Ph$,
CONHR,
CONHPh,
COY,
COPhCOOH,
COPhCOOR,
$(CH_2)_nCONHPh$,
$(CH_2)_nCONHPhR$,
SO_2Y;

n is an integer from 1 to 4;

R is lower alkyl;

R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SH, S_oX, and S_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl moiety of Formula I.

6. The compound of Claim 1 having the name 3-(2-thioxo-3-indolinyl)propanoic acid.

7. The compound of Claim 1 having the name 4-(2-thioxo-3-indolinyl)butanoic acid and pharmaceutically acceptable salts thereof.

8. The compound of Claim 1 having the name benzyl[N-phenyl 1-methylindolyl-3-carboxamide(2)]-disulfide.

9. The compound of Claim 1 having the name bis[indolyl-3-acetic acid-(2)]trisulfide.

10. The compound of Claim 1 having the name N-benzyl(2-thioxo-3-indolinyl)acetamide and pharmaceutically acceptable salts thereof.

11. The compound of Claim 1 having the name bis[indolyl-3-propanoic acid-(2)]disulfide and pharmaceutically acceptable salts thereof.

12. The compound of Claim 1 having the name 2,2'-dithiobis[3-(1-methyl-3-indolyl)propanoic acid] and pharmaceutically acceptable salts thereof.

13. The compound of Claim 1 having the name bis[ethylindolyl-3-propanoate-(2)]disulfide.

14. The compound of Claim 1 having the name 2,2'-dithiobis[methyl-3-(1-methyl-3-indolyl)-propanoate].

15. The compound of Claim 1 having the name bis[6-methylindolyl-3-propanoic acid-(2)]disulfide and pharmaceutically acceptable salts thereof.

16. The compound of Claim 1 having the name bis[ethyl-6-methylindolyl-3-propanoate(2)]-disulfide.

17. The compound of Claim 1 having the name bis[7-methylindolyl-3-propanoic acid-(2)]disulfide and pharmaceutically acceptable salts thereof.

18. The compound of Claim 1 having the name 2,2'-dithiobis[N-benzyl-3-(3-indolyl)propanamide].

19. The compound of Claim 1 having the name 2,2'-dithiobis[4-(1-methyl-3-indolyl)butanoic acid] and pharmaceutically acceptable salts thereof.

20. The compound of Claim 1 having the name bis[methyl 1-methylindolyl-3-butanoate-(2)]disulfide.

21. The compound of Claim 1 having the name bis[N-phenyl 1-methylindolyl-3-carboxamide(2)]-disulfide.

22. The compound of Claim 1 having the name bis[N-phenyl 5-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide.

23. The compound of Claim 1 having the name bis[N-phenyl 6-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide.

24. The compound of Claim 1 having the name bis[N-phenyl 7-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide.

25. The compound of Claim 1 having the name bis[N-methyl 1-methylindolyl-3-carboxamide(2)]-disulfide.

26. The compound of Claim 1 having the name bis[N-benzyl 1-methylindolyl-3-carboxamide(2)]-disulfide.

27. The compound of Claim 1 having the name bis[N-methylphenylsulfonyl)-2-indolyl]disulfide.

28. The compound of Claim 1 having the name bis[3-(4'-carboxybenzoyl)-1-methylindole-(2)]disulfide.

29. The compound of Claim 1 having the name bis[3-(4'-carbomethoxybenzoyl)-1-methylindole-(2)]-disulfide.

30. The compound of Claim 1 having the name methyl 3-(1-methyl-2-thioxo-3-indolinyl)propanoate.

31. The compound of Claim 1 having the name ethyl 3-(1-methyl-2-thioxo-3-indolinyl)propanoate.

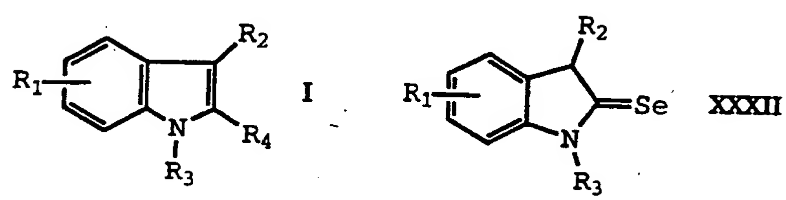
32. The compound of Claim 1 having the name N-benzyl 3-(2-thioxo-3-indolinyl)propanamide.

33. A method for inhibiting protein tyrosine kinase dependent disease in a mammal, comprising

administering to said mammal a pharmaceutical composition according to Claim 4.

34. A method for treating aberrant cell growth in a mammal, comprising administering to said mammal a pharmaceutical composition according to Claim 5.

35. 2-Selenoindole, 2-indolineselenone and selenide compounds of the group represented by the general Formulas I and XXXII



and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OCOR, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

C_{2-4} alkyl,
$(CH_2)_nCOOH$,
$(CH_2)_nCOOR$,
$(CH_2)_nCOR$,
$(CH_2)_nSO_2R$,
$(CH_2)_nSO_2NRR$,
$(CH_2)_nSO_2NHR$,
CH=CHCOOH,

$(CH_2)_nCH(OH)\text{-}COOH$,

$(CH_2)_nCH(NH_2)\text{-}COOH$,

$(CH_2)_nCONH_2$,

$(CH_2)_nCONHR$,

$(CH_2)_nCONRR$,

$(CH_2)_nCONHCH_2Ph$,

CONHR,

CONRR,

CONHPh,

COY,

COPhCOOH,

COPhCOOR,

$(CH_2)_nCONHPh$,

$(CH_2)_nCONHPhR$,

SO_2Y;

n is an integer from 1 to 4;

R is lower alkyl;

R_3 is a member selected from H, lower alkyl, and benzyl;

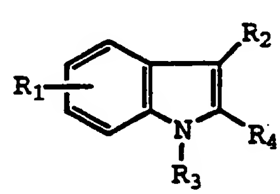
Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SeH, Se_oX, and Se_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-selenoindolyl moiety of Formula I.

36. A selenide compound according to Claim 35 selected from

2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid, t-butyl ester],
2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid],
2,2'-diselenobis[N,1-dimethyl-1H-indole-3-carboxamide],
2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1-methyl-1H-indole-3-carboxamide],
2,2'-diselenobis[N-methyl-1H-indole-3-carboxamide],
2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1H-indole-3-carboxamide],
2,2'-diselenobis[N-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide],
2,2'-diselenobis[1-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide],
[R-(R*,R*)]-2,2'-diselenobis[α-amino-N-(phenylmethyl)-1H-indole-3-propanamide], or
[S-(R*,R*)]-2,2'-diselenobis[α-amino-N-(phenylmethyl)-1H-indole-3-propanamide]
and pharmaceutically acceptable salts thereof.

37. A pharmaceutical composition useful for inhibition of protein tyrosine kinase dependent disease in a mammal, containing in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound selected from 2-selenoindole, 2-indolineselenone, and selenide compounds represented by the general Formulas I and XXXII



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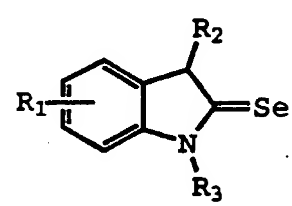


XXXII

and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

C_{2-4} alkyl,
$(CH_2)_nCOOH$,
$(CH_2)_nCOOR$,
$(CH_2)_nCOR$,
$(CH_2)_nSO_2R$,
$(CH_2)_nSO_2NRR$,
$(CH_2)_nSO_2NHR$,
CH=CHCOOH,
$(CH_2)_n\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}COOH$,
$(CH_2)_n\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{-}COOH$,
$(CH_2)_nCONH_2$,
$(CH_2)_nCONHR$,
$(CH_2)_nCONRR$,
$(CH_2)_nCONHCH_2Ph$,
CONHR,
CONRR,
CONHPh,
COY,
COPhCOOH,
COPhCOOR,
$(CH_2)_nCONHPh$,
$(CH_2)_nCONHPhR$,
SO_2Y;

n is an integer from 1 to 4;

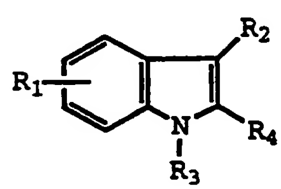
R is lower alkyl;

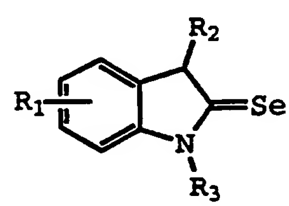
R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SeH, Se_oX, and Se_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-selenoindolyl moiety of Formula I.

38. A pharmaceutical composition useful for treating aberrant cell growth in a mammal containing in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound selected from 2-selenoindole, 2-indolineselenone, and selenide compounds represented by the general Formulas I and XXXII


I


XXXII

and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OR, CF_3, NO_2, NH_2, NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R_2 is a member selected from

C_{2-4} alkyl,
$(CH_2)_nCOOH$,
$(CH_2)_nCOOR$,
$(CH_2)_nCOR$,
$(CH_2)_nSO_2R$,
$(CH_2)_nSO_2NRR$,
$(CH_2)_nSO_2NHR$,
CH=CHCOOH,
$(CH_2)_nCH(OH)\text{-}COOH$,
$(CH_2)_nCH(NH_2)\text{-}COOH$,
$(CH_2)_nCONH_2$,
$(CH_2)_nCONHR$,
$(CH_2)_nCONRR$,
$(CH_2)_nCONHCH_2Ph$,
CONHR,
CONHPh,
COY,
COPhCOOH,
COPhCOOR,
$(CH_2)_nCONHPh$,
$(CH_2)_nCONHPhR$,
SO_2Y;

n is an integer from 1 to 4;

R is lower alkyl;

R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2, CONHR, CONRR, OR, or NHR group; and

R_4 represents SeH, Se_oX, and Se_oQ where o is 1, 2, or 3, X is a member selected from H, lower

alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-selenoindolyl moiety of Formula I.

39. The compound of Claim 35 having the name [R-(R*,R*)]-2,2'-diselenobis[α-amino-N-(phenylmethyl)-1H-indole-3-propanamide].

40. The compound of Claim 35 having the name [S-(R*,R*)]-2,2'-diselenobis[α-amino-N-(phenylmethyl)-1H-indole-3-propanamide].

41. The compound of Claim 35 having the name 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid, t-butyl ester].

42. The compound of Claim 35 having the name 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid].

43. The compound of Claim 35 having the name 2,2'-diselenobis[N,1-dimethyl-1H-indole-3-carboxamide].

44. The compound of Claim 35 having the name 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1-methyl-1H-indole-3-carboxamide].

45. The compound of Claim 35 having the name 2,2'-diselenobis[N-1-methyl-1H-indole-3-carboxamide].

46. The compound of Claim 35 having the name 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1H-indole-3-carboxamide].

47. The compound of Claim 35 having the name 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide].

48. The compound of Claim 35 having the name 2,2'-diselenobis[1-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide].

49. A method for inhibiting protein tyrosine kinase dependent disease in a mammal comprising administering to said mammal a pharmaceutical composition according to Claim 37.

50. A method for treating aberrant cell growth in a mammal, comprising administering to said mammal a pharmaceutical composition according to Claim 38.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/07272

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D209/30; C07D209/42; C07D405/14; C07D409/14
C07D401/14; C07D471/04; A61K31/40; A61K31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE vol. 1, 1987, pages 181 - 188 'A new preparation of N-aryl-1-alkyynesulphenamides and their thermal rearrangements into indoline-2-thiones' *see compounds of examples 29,30 and 32*	1
X	TETRAHEDRON vol. 42, 1986, pages 5879 - 5886 'Synthesis of debromo-8,8a-dihydroflustramine C, a model synthesis towards amauromine' cited in the application *see compound number 12, page 5881*	1

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° Special categories of cited documents : [10]

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

1

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 NOVEMBER 1993	-9. 12. 93
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	SCRUTON-EVANS I.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	TETRAHEDRON LETTERS vol. 31, 1990, pages 7229 - 7232 'Selectivity in the Thiocyanation of 3.alkylindoles: An unexpectedly easy access to 2-isothiocyano derivatives' cited in the application ---	1-32
T	JOURNAL OF MEDICINAL CHEMISTRY vol. 36, 1993, pages 2459 - 2469 'Tyrosine kinase inhibitors' ---	1-32, 35-48
A	WO,A,9 113 055 (FARMITALIA CARLO ERBA S.R.L) 5 September 1991 ---	1-32, 35-48
P,A	US,A,5 196 446 (YISSUM RESEARCH DEVELOPMENT CO. OF THE HEBREW UNIVERSITY OF JERUSALEM) 23 March 1993 -----	1-32

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9307272
SA 78016

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/11/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP-A- 0470221	12-02-92
		JP-T- 4506081	22-10-92
US-A-5196446	23-03-93	AU-A- 7756891	11-11-91
		EP-A- 0527181	17-02-93
		WO-A- 9116305	31-10-91

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82